FDA Executive Summary

VertiFlex® Superion® InterSpinous Spacer

Prepared for the
February 20, 2015, Meeting of the
Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

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INTRODUCTION

The subject of this Executive Summary is the VertiFlex® Superion® InterSpinous Spacer (ISS) premarket approval (PMA) application, P140004. The Superion® ISS (also referred to as Superion®) is an "H"-shaped, titanium device which sits between two adjacent spinous processes in the lumbar spine. The device is placed via percutaneous or minimally-invasive surgical techniques. When implanted in the appropriate size, it is designed to provide distraction of the spinous processes to open the central spinal canal, lateral recess, and/or neural foramina, and inhibit or restrict extension at the affected spinal level. By doing so, narrowing of the central spinal canal, lateral recess and/or foramina that contributes to the symptoms of lumbar stenosis (i.e., neurogenic claudication) is eliminated or reduced as the pressure placed on the cauda equina and nerve roots is relieved, while neural compression which is typically caused or exacerbated by extension is prevented. This PMA application has been reviewed by staff in the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) (also referred to as the Agency). Your time and effort in the review of this PMA application is greatly appreciated.

Rationale for Presentation to the Panel

The FDA is presenting this PMA application to the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee for the following reasons:

- The VertiFlex® Superion® InterSpinous Spacer (ISS) exhibits a higher rate of spinous process fractures than other non-fusion interspinous process devices intended to treat lumbar spinal stenosis, even when "healed" fractures are considered. In the IDE clinical trial, 16.3% (31/190) Superion® ISS modified Intent-to-Treat (mITT) subjects had a spinous process fracture identified at any time point , in contrast with 8.5% (17/201) X-STOP® mITT control subjects. Of these subjects with observed fractures, the majority (27/31 - Superion®; 14/17 - X-STOP®) of the fractures in both cohorts occurred within 6 weeks of implantation. It was also noted that based on information from the independent radiographic analysis, 32.3% (10/31) Superion® ISS subjects with spinous process fractures and 41.2% (7/17) X-STOP® subjects with spinous process fractures exhibited healing of the spinous process fractures by 24 months.
- The Agency is unclear regarding the clinical significance of a 16.3% fracture rate in the investigational group, given that the Superion® ISS relies on the intact spinous processes for its treatment effect, and requests Orthopaedic and Rehabilitation Devices Panel input on this issue.
- The Agency is aware of reports in the literature [1-5] of spinous process fractures occurring with this device class. Intuitively, it would seem that such pathology would result in pain and/or functional deficit. However, data has been submitted by the sponsor to support the claim that spinous process fractures are often asymptomatic in subjects implanted with the Superion® ISS, and therefore of no clinical significance. This conclusion is based on Zurich Claudication Questionnaire (ZCQ), Visual Analog Scale (VAS), and Oswestry Disability Index (ODI) data.
- The Agency asserts that the Superion® ISS is dependent on the integrity of the spinous processes to produce its treatment effect. Accordingly, it is reasonable to consider that a fracture involving the spinous process at the operative level would impact the effectiveness of the device. It is unclear whether the data presented by the sponsor are adequate to assess the clinical significance of these fractures.
- The data submitted to the Agency demonstrated that additional procedures were performed during implantation of both the investigational and control devices. A total of 9 investigational

subjects (11 procedures) and 11 control subjects (16 procedures) had such procedures. These procedures included facet de-bulking (2 control subjects), osteophyte removal (3 investigational subjects, 3 control subjects), and soft tissue removal (6 investigational subjects, 13 control subjects). The sponsor stated these procedures were performed to facilitate implant insertion. However, these procedures have the potential to provide neural decompression at the surgical site. It is not clear how to differentiate the treatment effect of the device from any treatment effect secondary to these additional procedures.

- Although the subject device and the control device exhibit similar overall failure rates, the subject device failure rate is driven by spinous process fractures; whereas the control device failure rate is driven by device migrations and dislodgements. The comparability of these events (spinous process fractures versus device migrations and device dislodgements) and the clinical sequelae resulting from each type of event remain unclear based on information contained in the sponsor's submission.
- The overall success rate of the device, while non-inferior to the control device, is low for both the experimental and control groups. The Agency is aware of literature which supports spinal decompression as the appropriate comparator for assessment of outcomes associated with use of non-fusion interspinous process devices [6]. The Agency is seeking input from the external experts of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee to assess whether the probable benefits of the use of the Superion® ISS outweigh the probable risks when this device is used in the indicated population in accordance with the proposed instructions for use.

FDA Questions to the Panel

The FDA would like the Panel to provide responses to a series of questions regarding the safety and effectiveness data presented in the PMA application. These questions are located in the "FDA Panel Questions" section of the Panel package, and Panel input will be solicited at the February 20, 2015, Panel meeting.

BACKGROUND INFORMATION

Applicant Name and Address

VertiFlex®, Incorporated
1351 Calle Avanzado
San Clemente, California 92673

Indications for Use

The following Indications for Use are proposed by the sponsor in the PMA application (P140004):

"The Superion® ISS is intended to treat skeletally mature subjects suffering from pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis, confirmed by X-ray, MRI and/or CT evidence of thickened ligamentum flavum, narrowed lateral recess, and/or central canal or foraminal narrowing. The Superion® ISS is indicated for those subjects with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with

or without back pain. The Superion® ISS may be implanted at one or two adjacent lumbar levels in subjects in whom treatment is indicated at no more than two levels, from L1 to L5."

Contraindications

The sponsor proposes that the use of the Superion® ISS be contraindicated in the following cases:

- an allergy to titanium or titanium alloy;
- spinal anatomy or disease that would prevent implantation of the device or cause the device to be unstable in situ, such as:
    - significant instability of the lumbar spine, e.g., isthmic spondylolisthesis or degenerative spondylolisthesis greater than grade 1 (on a scale of 1 to 4);
    - an ankylosed segment at the affected level(s);
    - acute fracture of the spinous process, pars interarticularis, or laminae fracture (unilateral or bilateral);
    - significant scoliosis (Cobb angle >10 degrees);
- *Cauda equina* syndrome defined as neural compression causing neurogenic bladder or bowel dysfunction;
- diagnosis of severe osteoporosis, defined as bone mineral density (from DEXA scan or equivalent method) in the spine or hip that is more than 2.5 S.D. below the mean of adult normals in the presence of one or more fragility fractures; and
- active systemic infection or infection localized to the site of implantation.

The FDA will be recommending a modification of the proposed contraindications to highlight an ankylosed segment at the affected level as a contraindication unrelated to spinal instability, as well as clarification of the definition of severe osteoporosis.

Warnings and Precautions

The sponsor proposes that the following warnings and precautions be included in the labeling for the Superion® ISS:

- The Superion® ISS must be placed in the concavity between the spinous processes. If correct placement of the implant cannot be achieved due to variant anatomy, the surgeon should consider aborting the procedure because incorrect placement may result in device dislodgement, particularly if the patient experiences a traumatic event.
- The effect of multiple deployments, upon implant strength, has not been determined. In the event that a Superion® ISS must be deployed, closed, and redeployed for repositioning more than three times during a procedure, the spacer should be discarded, and a new device used.
- Radiological evidence of stenosis must be correlated with the patient's symptoms before the diagnosis can be confirmed.
- If the spinous processes at the affected levels are not distracted in flexion, the Superion® ISS may not be indicated.
- The safety and effectiveness of the Superion® ISS has not been studied in subjects with the following conditions: axial back pain without leg, buttock, or groin pain; symptomatic lumbar spinal stenosis at more than two levels; prior lumbar spine surgery; significant peripheral neuropathy; acute denervation secondary to radiculopathy; Paget's disease; vertebral

metastases; morbid obesity; pregnancy; a fixed motor deficit; angina; active rheumatoid arthritis; peripheral vascular disease; advanced diabetes; or other systemic disease that may affect the patient's ability to walk.

- Implantation of the Superion® ISS should be performed only by qualified and experienced spinal surgeons having specific training in the implantation of the device, because this is a technically demanding procedure presenting risk of serious injury to the patient.
- Surgeons should not implant the Superion® ISS until receiving adequate training in surgical technique. Inadequate training may result in poor patient outcomes and/or increased rates of adverse events.
- A stress fracture of the spinous process may occur if strenuous activity is resumed too soon postoperatively.

Device Description

The Superion® ISS (Figure 1) is intended to mitigate the symptoms of moderate lumbar spinal stenosis, and specifically neurogenic intermittent claudication (NIC), by preventing narrowing of the central spinal canal, lateral recess, and/or neural foramina and compression of the affected neural elements (i.e., cauda equina and lumbar nerve roots) in extension. The Superion® ISS achieves its treatment effect principally by serving as an "extension-blocker." Typically, NIC is relieved with flexion, which enlarges the lumbar central spinal canal, lateral recess, and/or neural foramina. In contrast, NIC manifests when a patient is upright and the lumbar spine is positioned in mild extension, causing narrowing of the space available for the neural structures. When the Superion® ISS is positioned between adjacent spinous processes, it is believed that the implant prevents narrowing of the space available for the neural structures, thereby reducing or preventing the return of symptoms.

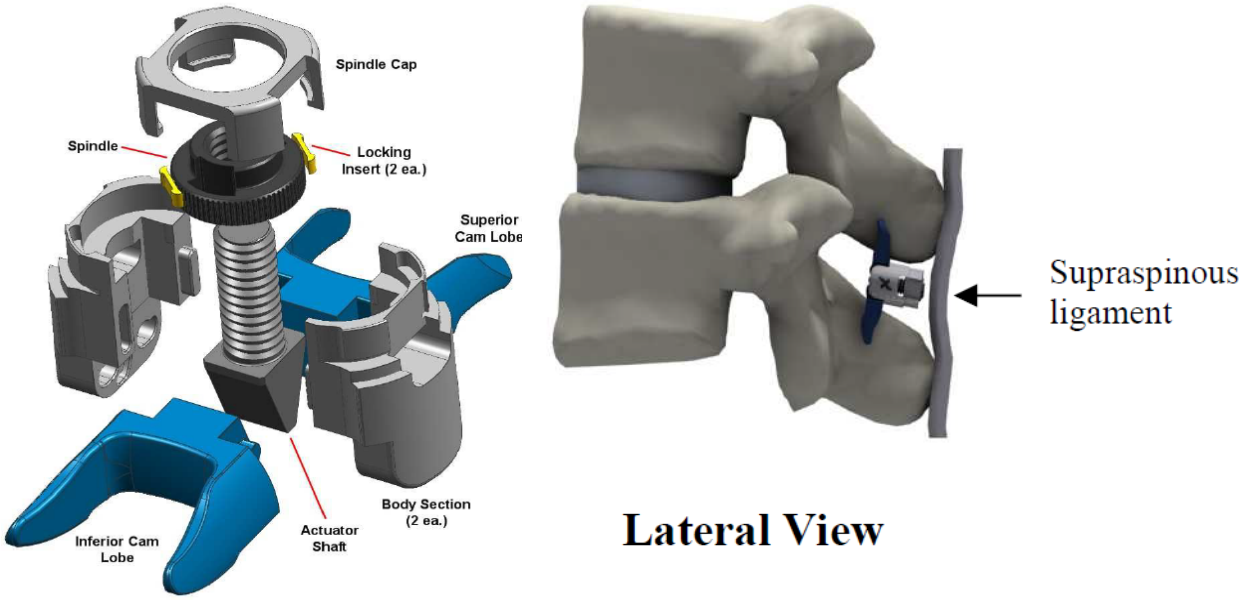


Figure 1: Exploded schematic and positioning of Superion® ISS

The Superion® ISS has been produced in two (2) distinct design iterations. The first version, p/n 100-00XX (the original design), described in the original IDE application submitted on July 9, 2007, employed a different locking mechanism than the version employed in the U.S. clinical trial (p/n 100-01XX), and was distributed commercially outside the United States for a brief period of less than 1 year. It was not employed in the U.S. clinical trial. Several of the non-clinical tests used to support IDE approval were conducted using this initial design. Thereafter, as described in a December 28, 2007 correspondence submitted to the Agency, the sponsor introduced a device design with a distinctly different actuation and locking mechanism. It was this version that was used exclusively in the U.S. clinical trial approved under IDE G070118.

The Superion® ISS is manufactured entirely from Ti-6Al-4V alloy. Each device consists of an implant body, two cam lobes, and an internal actuating mechanism by which the cam lobes are rotated to the deployed position using manual instruments provided by VertiFlex® for use with the Superion® ISS. Implants are available in five (5) sizes, ranging from 8mm to 16mm, in 2mm increments. Implants are color-coded via an anodization process to designate size, and are also laser-etched with the implant size.

The implant consists of a cylindrical body, at the distal end of which are located two forked, or saddle-shaped cam lobes, or "wings." These cam lobes are aligned with the implant body axis to permit introduction of the device into the interspinous process space through the delivery cannula. During implantation, manual instrumentation is used to rotate these components 90° to positions perpendicular to the implant body axis as shown in Figure 2. In the open, deployed state, the cam lobes engage the lateral surfaces of two adjacent spinous processes, such that the inferior edge of the superior spinous process and the superior edge of the inferior spinous process rest within the saddles of the two cam lobes.

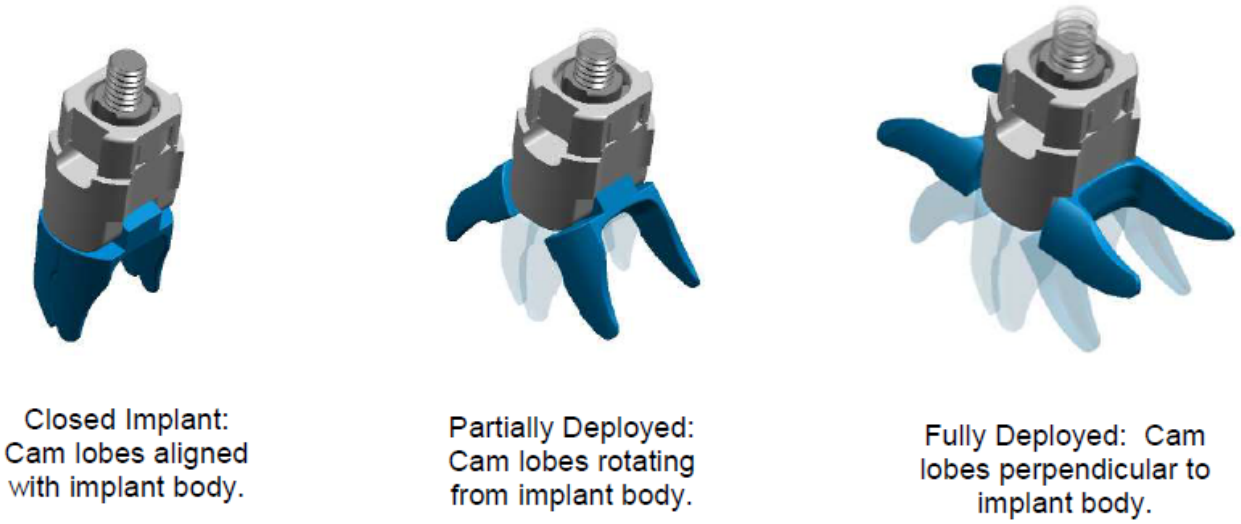


Figure 2: Mechanism of action of Superion® ISS

NON-CLINICAL EVALUATION OF THE SUPERION® INTERSPINOUS SPACER

Non-Clinical Testing

The following non-clinical testing has been conducted and repeated on all design iterations of the Superion® ISS device (i.e., both p/n 100-00XX and p/n 100-01XX):

- Static Axial Compression
- Dynamic Axial Compression
- Static Torsion
- Dynamic Torsion
- Deployment Under Load
- Cadaveric Assessment of Mean Resultant Moment
- Cadaveric Assessment of Mean Discrete Angular Displacement
- Cadaveric Assessment of Overall Motion of Spinal Segment
- Cadaveric Assessment of Intradiscal Pressure
- Cadaveric Assessment of Role of Supraspinous Ligament in Biomechanical Stability
- MR Compatibility Testing

No concerns were identified in any of these non-clinical tests.

Biocompatibility

The Superion® InterSpinous Spacer implants are manufactured from Titanium-6Al-4V ELI alloy conforming to the recognized material standard ASTM F136, *Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications*. This material is well-accepted within the medical device industry as being safe for use as an orthopedic implant and comprises many commercially-available devices, including permanent spinal implants and joint prostheses, among others. Further, the ASTM Standard itself supports the biocompatibility of the material in its Appendix X2**,** wherein it notes that the alloy has been used successfully in human implant applications in bone and soft tissue for a long period of time, and elicits "an acceptable level of biological response."

Based on the above information, it was determined that additional biocompatibility testing was not necessary, and no further testing was conducted.

CLINICAL STUDY DESCRIPTION

History

Lumbar spinal stenosis (LSS) is a disease most commonly associated with the aging population and degeneration of the spinal column. As the spine degenerates, it may lead to narrowing of the central spinal canal, lateral recess, and/or neural foramina - the spaces through which major neural elements pass. This narrowing may or may not result in clinical symptoms. As early as the 1950's, it was recognized that structural narrowing of the vertebral canal could compress the cauda equina and produce intermittent neurogenic claudication symptoms. Symptoms of neurogenic claudication include buttock pain and/or leg pain (and occasionally weakness) on walking or standing, which is relieved by

sitting or spinal flexion. The disease can be mitigated, but not prevented or cured. The current standard of care [7, 8] and available treatment alternatives include:

Non-surgical

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Analgesics
- Oral and epidural steroids
- Rest
- Exercise
- Physical therapy
- Bracing

Surgical

- Decompressive procedures (laminectomy, hemilaminectomy, foraminotomy, etc.)
- Indirect decompression with other interspinous distraction devices (X-STOP®)
- Direct decompression with non-fusion posterior stabilization devices (coflex®)
- Decompression plus postero-lateral fusion with or without the use of adjunctive pedicle screw spinal instrumentation systems

Introduction

The IDE clinical study (G070118) was designed as a multicenter (33 sites [31 active]), prospective, randomized, controlled (with X-STOP®), non-inferiority trial with up to 470 subjects (including up to 75 non-randomized training cases). An adaptively selected sample size, as well as a Bayesian statistical plan, was used to assess the data. Patient enrollment for the Superion® ISS clinical trial began in June 2008, with the first implant of a non-randomized training subject on June 26, 2008. Enrollment of the full allowance of 470 subjects was completed on December 12, 2011. The total number of subjects includes 30 training subjects and 440 randomized subjects. Of the training subjects, 28 were treated, and 2 were post-consent screen failures that did not proceed to treatment. Of the 440 randomized subjects, 49 are post-consent screen failures that did not proceed to treatment, including 28 in the Superion® arm and 21 in the control arm. Of the remaining 391 randomized subjects, 190 were randomized to the Superion® ISS cohort, and 201 to the X-STOP® cohort. As of February 14, 2012, all subjects had been treated.

The X-STOP® was chosen as the study control since this device is PMA-approved for a similar intended patient population and Indications for Use as the Superion® ISS. The IDE clinical trial was designed to test for non-inferiority, with the purpose to demonstrate that the success rate of the study group receiving the Superion® ISS is not inferior to the success rate observed in the X-STOP® control group, and that the Superion® ISS is safe when used in the treatment of moderately impaired LSS subjects. Overall success at 24 months is based on improvement documented in the Zurich Claudication Questionnaire (ZCQ), and absence of major implant complications or surgical interventions.

Data from 419 study subjects was entered into the electronic database as of December 31, 2013. This data included 28 training subjects, 190 investigational (Superion® ISS) subjects, and 201 control (X-STOP®) subjects. All results are based on this reported data unless noted otherwise. The study

population has a mean age of 67 years and is 61.6% male and 38.4% female. The study population has a mean BMI of 29.6.

Purpose

The purpose of this study was to demonstrate that the success rate of the study group receiving the Superion® ISS is not inferior to the success rate observed in the X-STOP® control group, and that the Superion® ISS is safe when used in the treatment of moderately impaired LSS subjects.

Study Design

The sponsor conducted a randomized, controlled, prospective, multicenter, pivotal clinical trial comparing the Superion® ISS to the X-STOP®. The study enrolled subjects diagnosed with moderate spinal stenosis, and evaluated success based on clinical and radiographic endpoints at regular, specified intervals. The sponsor provided 24-month follow-up on all enrolled subjects, as well as 36 month follow-up on greater than 90% of those subjects theoretically due for their Month 36 clinical visit (74% of total subjects).

Control

The control group in this study consisted of the X-STOP®, an FDA approved device indicated for the treatment of subjects aged 50 years or older, experiencing moderate symptoms of neurogenic intermittent claudication secondary to a confirmed diagnosis of LSS. The X-STOP® implant is a titanium metal implant designed to fit between the spinous processes in the lumbar spine. The control was concurrent and randomized according to 1:1 randomization ratio.

Surgical Procedures Used to Implant the Investigational and Control Devices

<u>Superion®</u>

The Superion® device is implanted posteriorly through a minimally invasive approach (requires a 12 – 15mm midline posterior lumbar incision), using fluoroscopic guidance to insert Dilator #1; or a mini-open approach which involves direct visualization and open dissection of the supraspinous ligament. First, an aperture is created in the supraspinous ligament. Next dilation is performed (Dilator #1, Dilator #2) to permit insertion of a cannula. An Interspinous Reamer can be used to further prepare the interspinous space for delivery of the implant. Orientation and appropriate sizing for the device are determined and confirmed with fluoroscopy. The implant is loaded onto the inserter, which is introduced through the cannula. The wings are then deployed under fluoroscopic guidance. Final implant position is confirmed with fluoroscopy. Repair of the supraspinous ligament can be performed, if indicated, prior to closure.

<u>X-STOP®</u>

The X-STOP® device is implanted through an open midline posterior incision. The paraspinal muscles are elevated from the spinous processes and lamina, preserving the supraspinous ligament. The interspinous ligament is pierced deep to the supraspinous ligament, and the interspinous space is initially distracted using curved dilators. The appropriate size of the definitive implant is determined using a sizing distractor. The appropriately sized spacer is placed onto an inserter and inserted in the

interspinous space from a medial to lateral direction. Next, the wings of the device are inserted and attached to the spacer by means of a locking screw. Implant position is confirmed with radiographs or fluoroscopy.

Enrollment Criteria

Listed below are the enrollment criteria as defined in the IDE protocol and excerpted from the PMA submission.

Inclusion	Exclusion
1. Male or female subjects ≥ 45 years of age	1. Axial back pain only
2. Persistent leg/buttock/groin pain, with or without back pain, that is relieved by flexion activities (example: sitting or bending over a shopping cart)	2. Fixed motor deficit
3. Subjects who have been symptomatic and undergoing conservative care treatment for at least 6 months	3. Diagnosis of lumbar spinal stenosis which requires any direct neural decompression or surgical intervention other than those required to implant the control or investigational device
4. Diagnosis of degenerative spinal stenosis of the lumbar spine, defined as the narrowing of the midline sagittal spinal canal (central) and/or narrowing between the facet superior articulating process (SAP), the posterior vertebral margin (lateral recess), and the nerve root canal (foraminal)	4. Unremitting pain in any spinal position
5. Radiographic confirmation of at least moderate spinal stenosis which narrows the central, lateral, or foraminal spinal canal at one or two contiguous levels from L1-L5. Moderate spinal stenosis is defined as 25% to 50% reduction in lateral/central foramen compared to the adjacent levels, with radiographic confirmation of any one of the following: - Evidence of thecal sac and/or cauda equina compression - Evidence of nerve root impingement (displacement or compression) by either osseous or non-osseous elements - Evidence of hypertrophic facets with canal encroachment	5. Significant peripheral neuropathy or acute denervation secondary to radiculopathy
6. Must present with moderately impaired Physical Function (PF) defined as a score of > 2.0 of the Zurich Claudication Questionnaire (ZCQ)	6. Lumbar spinal stenosis at more than two levels determined pre-operatively to require surgical intervention
7. Must be able to sit for 50 minutes without pain and to walk 50 feet or more	7. Significant instability of the lumbar spine as defined by ≥ 3mm translation or ≥ 5° angulation
8. Subjects who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained	8. Sustained pathologic fractures of the vertebrae or multiple fractures of the vertebrae and/or hips

9. Subjects, who, in the opinion of the Clinical Investigator, are able to understand this clinical, investigation, cooperate with the investigational procedures and are willing to return for all the required post-treatment follow-ups.	9. Spondylolisthesis or degenerative spondylolisthesis greater than grade 1 (on a scale of 1-4)
	10. Spondylolysis (pars fracture)
	11. Degenerative lumbar scoliosis with a Cobb angle of > 10° at treatment level
	12. Osteopenia or osteoporosis. To confirm eligibility, at the Clinical Investigator's discretion, the following subjects may have a DEXA scan performed: - women 65 or older - menopausal women < age 65 For subjects with major risk factors for or diagnosed with osteoporosis or osteopenia, DEXA is required, exclusion is defined as a DEXA bone density measurement T score ≤ -2.5
	13. Morbid obesity, defined as Body Mass Index (BMI) greater than 40 kg/m2
	14. Insulin-dependent diabetes mellitus
	15. Significant peripheral vascular disease (diminished dorsalis pedis or tibial pulses)
	16. Prior surgery of the lumbar spine
	17. Cauda equina syndrome (defined as neural compression causing neurogenic bowel or bladder dysfunction)
	18. Infection in the disc or spine, past or present
	19. Evidence of active (systemic or local) infection at time of surgery
	20. Active systemic disease such as AIDS, HIV, hepatitis, etc.
	21. Paget's disease at involved segment or metastasis to the vertebrae, osteomalacia, or other metabolic bone disease
	22. Currently undergoing immunosuppressive therapy or long-term steroid use
	23. Known allergy to titanium or titanium alloys
	24. Tumor in the spine or a malignant tumor, except for basal cell carcinoma
	25. Known or suspected history of alcohol and/or drug abuse
	26. Prisoner or transient
	27. Life expectancy less than two years

	28. Angina, active rheumatoid arthritis, or any other systemic disease that would affect the subject's welfare or outcome of the clinical investigation
	29. Any significant psychological disturbance past or present, psychotic or neurotic that could impair the consent process or ability to complete subject self-report questionnaires
	30. Involved in pending litigation of the spine or worker's compensation related to the back
	31. Enrolled in the treatment phase of another drug or device clinical investigation (currently or within past 30 days)
	32. Congenital defect of the spine
	33. Pregnant or lactating

Note: According to Inclusion Criteria #5, all imaging used to confirm LSS was completed within 3 months prior to enrollment. Radiographic confirmation of LSS could have included MRI and/or CT. In the case of a transitional L5/L6 segment with a sufficiently prominent L6 spinous process, these subjects may have been included by requesting a deviation from the sponsor.

Assessment Instruments and Follow-Up Schedule

Table 1 outlines the assessments planned for each follow-up visit.

Table 1: Patient assessment schedule

	Appendix A. Visit Schedule								
	Screening -Baseline	**Surgical Treatment**	**Discharge (±0-7 days)**	**6-week (±2 weeks)**	**3-month (±2 weeks)**	**6-month (±1 month)**	**12-month (±2 months)**	**18-month (±2 months)**	**24-month[c] (±2 months)**
Study Visit Window		Day 0	0-7 days	4-8 weeks	10-14 weeks	5-7 months	10-14 months	16-20 months	22-26 months
Signed Informed Consent	X								
Demographic Information	X								
Complete History & Physical	X								
Randomization	X								
Standing AP & Lateral Lumbar Spine X-rays	X[a]		X	X	X	X	X	X	X
Flexion / Extension Lateral Lumbar Spine X-rays	X[a]			X	X	X	X	X	X
Lumbar Spine MRI/CT Scan	X[a]								
DEXA Scan[b]	As needed								
SF-12 –Health Survey (v2)	X			X	X	X	X	X	X
Zurich Claudication Questionnaire (ZCQ)	X			X	X	X	X	X	X
Oswestry Disability Index (v2)	X			X	X	X	X	X	X
Neurological Status	X		X	X	X	X	X	X	X
Visual Analogue Scale	X		X	X	X	X	X	X	X
VertiFlex® Patient Satisfaction Questionnaire				X	X	X	X	X	X
Assess Adverse Events		X	X	X	X	X	X	X	X

Surgical Assessment

The following information was planned to be collected at the time of surgery:

- Date of admission
- Date of surgery
- Type of anesthesia
- Level(s) treated
- Device Information
- Operative Time
- Estimated Blood Loss
- Intra-operative Adverse Events

Study Endpoints

The study was designed with the following primary and secondary endpoints, taken directly from the approved IDE protocol and subsequent Pre-Submission feedback (Q130906) prior to submission of the PMA. The endpoints are the same as those used in the PMA analysis.

Primary Composite Endpoint

An individual subject will be considered a success if they meet all of the following conditions at the 24 month follow-up:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the following for at least two of three domains of the Zurich Claudication Questionnaire (ZCQ):
  - Improvement in physical function by ≥ 0.5 points
  - Improvement in symptom severity by ≥ 0.5 points
  - "Satisfied" or "somewhat satisfied" as defined by a score of ≤ 2.5 points on the patient satisfaction domain
- No re-operations, removals, revisions, or supplemental fixation at the index level(s)
- No major implant or procedure-related complications defined as:
  - No dislodgement, migration, or deformation of the implant
  - New or persistent worsened neurological deficit at the index level
  - Spinous process fracture(s)
  - Deep infection, death or other permanent disability attributed to the device
- No clinically significant confounding treatments such as:
  - Epidural steroid injections or nerve block procedures at the index level(s)
  - Spinal cord stimulators or rhizotomies

We will be asking the Panel to comment on the overall success definition and time point assessment utilized in this clinical trial.

Secondary Endpoints

The secondary endpoints of this investigation are:

- To demonstrate the superiority of Superion® ISS to X-STOP® in effectively treating moderately impaired LSS subjects as measured by 24 months postoperative overall success rates
- VertiFlex® Patient Satisfaction Survey – percent of subjects scoring ≤ 2.5 on a 4 point scale
- Oswestry Disability Index (ODI) Version 2 – compared to baseline, 15 point improvement (reduction in score) is considered clinically significant
- Visual Analogue Scale (VAS Leg and VAS Back) - compared to baseline, an improvement in back pain of 20 mm (on a 100 mm scale) is considered clinically significant
- To evaluate generic health status pre- and postoperatively using the SF-12 Short Form Health Survey, Version 2
- To evaluate maintenance of distraction defined by ≤ 4 mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 6 weeks and 24 months postoperatively

Other Endpoints

- Length of hospital stay
- Operative time
- Estimated blood loss
- Work status and time to return to work or normal activities of daily living (ADL)

- Type of anesthesia
- Rehabilitation utilization (concomitant treatments)
- Analgesic and Narcotic use

Analysis Populations

Initially there were three analysis populations defined for this study: the Intent-to-Treat (ITT) population, the As-treated (AT) population, and a Per Protocol (PP or Evaluable) population. These populations, as defined by the sponsor, are noted below.

- "*Intent-to-Treat (ITT) Population:* The ITT patient population will include all subjects randomized, where subjects will be classified by the group in which they are randomized, regardless of the treatment received.
- *As-treated (AT) Population:* The AT patient population will include all subjects treated, classified according to the treatment actually received.
- *Per protocol (PP) Population:* The PP patient population will include all subjects with 24-month follow-up data and no major protocol deviations and subjects that failed before 24 months."

The safety data analyses were conducted on the AT population. The primary composite endpoint (effectiveness) analyses were conducted on the ITT and PP populations. The ITT population was to serve as the primary population for the composite endpoint analysis.

The sponsor subsequently submitted IDE Supplement 016 on July 3, 2009, (which was approved), seeking to modify the definition of the ITT population as follows:

- "*Intent-to-Treat (ITT) Population:* The ITT patient population will include all subjects randomized, and have an anesthesia start time, where subjects will be classified by the group in which they are randomized, regardless of the treatment received.
- *Modified Intent-to-treat patient population (mITT):* The mITT patient population will include all subjects randomized and having an anesthesia start time, where subjects will be classified by the group in which they are randomized. Subjects with an anesthesia start time, but that do not receive a device, or receive the wrong device, will be failures. Note that the mITT population was the same as the ITT and served as the primary population for the final composite endpoint analysis for this PMA."

STATISTICAL ANALYSIS PLAN

Planned and Actual Sample Size

This clinical study was designed as a Bayesian adaptive trial with a minimum of 250 evaluable subjects and a maximum of 350 evaluable subjects, with an additional adjustment for loss-to-follow-up of 15%. The sponsor reports that the criteria for stopping accrual were not met at either the 250- or 300-patient interim look. The final sample size in the randomized mITT population consisted of 190 Superion® ISS and 201 X-STOP® subjects (391 total subjects). This is close to the maximum planned sample size, which would have been 412 total subjects after adjustment for loss-to-follow-up.

Study Hypotheses and Study Success Criteria

The primary hypothesis of this randomized controlled trial was that the clinical performance of the Superion® ISS is non-inferior to the clinical performance achieved with the active control, X-STOP®. The study endpoint was the rate of overall subject success at 24 months. A subject was considered a success if they were a success on each of the four individual primary outcome criteria. The hypotheses tested for this primary study endpoint are as follows:

H_0: *Superion®* ISS overall success rate is inferior

(*Superion®* rate – Control rate < -Δ)

H_A: *Superion®* ISS overall success rate is non-inferior

(*Superion®* rate – Control rate ≥ -Δ)

A Bayesian approach was used. If the posterior probability of the alternative hypothesis was at least 95.8%, using non-informative uniform (Beta[1,1]) priors for each success rate then the claim of non-inferiority would be made. The choice of non-inferiority margin, Δ (i.e., delta) was 10% for the overall subject success rate. The value of 0.958 was selected to control the type I error of this design (type 1 error less than 0.05).

An adaptive sample size approach was used, with a maximum of 350 evaluable subjects and a minimum of 250 subjects. The operating characteristics of the adaptive design demonstrate 86.3% power when the Superion® ISS group was superior to the Control group by 5% and 73.6% power when the advantage is 2.5%. In these calculations, the Control was assumed to have a 65% success rate.

Interim Analyses

The Statistical Analysis Plan (SAP) specified two interim looks after 250 and 300 subjects had been accrued. The purpose of these looks was to stop accrual if the interim results looked sufficiently promising or to stop for futility if result were sufficiently bad. However, when the looks were conducted, the interim study results did not meet the criteria for ceasing study enrollment, or for stopping for futility. Therefore, the study enrollment continued to the maximum sample size of 350 evaluable subjects.

Length of Treatment and Follow-up

The Superion® ISS and X-STOP® are both intended to be implanted at one initial treatment visit. The sponsor stated, “Subjects had follow up examinations at Discharge, 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months, with annual follow-up thereafter until the last subject reached 24 months.” Note that the 18-month visit was added after conditional approval of the study in IDE (G070118) Supplement 022.

Randomization

A computer generated random list (Master Randomization List) of treatment assignments, blocked and stratified (gender and number of affected vertebral levels), was created using a 1:1 stratified scheme for

each investigational site. These procedures were designed to balance the study groups for these factors, both overall and within investigational sites.

Blinding

The sponsor stated that the surgeon was blinded until after all baseline visit tests were performed and the subject was confirmed to meet all inclusion and exclusion criteria. According to the sponsor, study subjects were blinded until the end of the study, although there was difficulty in keeping the subjects blinded following surgery, as the incision location and pattern was different for the two devices. While the subjects were never told pre-operatively what treatment they were getting, the study subjects were asked to guess their treatment assignment at the 24-month visit, and these results show that almost all subjects had figured out their treatment at some point during the course of the 2 years. While the sponsor states that the incision location and pattern were different, from the surgical technique it appears that both procedures require a small midline lumbar incision and, therefore, the Agency does not feel this would be the primary reason for a patient figuring out their treatment.

Protocol Deviations

Major protocol deviations were defined as violations of inclusion and/or exclusion criteria, and informed consent violations. In the randomized cohort, the sponsor reports thirty-four (34) inclusion/exclusion violations, and five (5) consent violations in thirty-three (33) subjects. Subjects with inclusion/exclusion deviations were excluded from the Per-Protocol (PP) analysis unless the site received a waiver from the sponsor. A total of 19 subjects (10 Superion® and 9 X-STOP®) were excluded for having inclusion/exclusion violations without a waiver. Also, a total of 11 subjects (3 Superion® and 8 X-STOP®) received sponsor waivers.

The sponsor stated that minor protocol deviations included visits out-of-window and incomplete follow-up, such as partial completion of a questionnaire.

Subgroup Analyses

The sponsor has provided analyses of the primary and secondary safety and effectiveness endpoints by 1-level and 2-level, and for continuous variables by subgroups defined by Weight, Age, BMI, Height and Sex. In addition, the sponsor has reported exploratory analyses defined by the following: spinous process fracture: yes versus no; migrations/dislodgment: yes versus no; central versus lateral stenosis; spondylolisthesis: yes versus no; smoking versus non-smoking; spinal level; general versus local anesthesia; supraspinous ligament repair: yes versus no; surgical approach; original versus new instrumentation set; bone-implant interface changes: “none” versus “present”; orthopedic co-morbidities: yes versus no; site size; and post-operative care: “conservative care” versus “other.”

Bayesian Considerations

The statistical analysis of the primary endpoint is Bayesian, and makes use of Bayesian multiple imputations to handle the missing data. Note, however, that only non-informative priors were used in the primary analysis. In addition, there were two planned Bayesian interim analyses for purposes of sample size adaptation. However, accrual was not stopped at either interim analysis.

In addition to the primary Bayesian data presentation, the sponsor makes extensive use of frequentist methods, in particular p-values, for the secondary and subgroup analyses. It is not unusual to mix Bayesian and frequentist methods. However, as many of the analyses which follow were not pre-specified or suffer from multiplicity, the accompanying p-values should be considered exploratory and meant only to give an indication of the relative strength of the statistical results. They should not be interpreted as confirmatory.

CLINICAL STUDY RESULTS

Patient Accounting

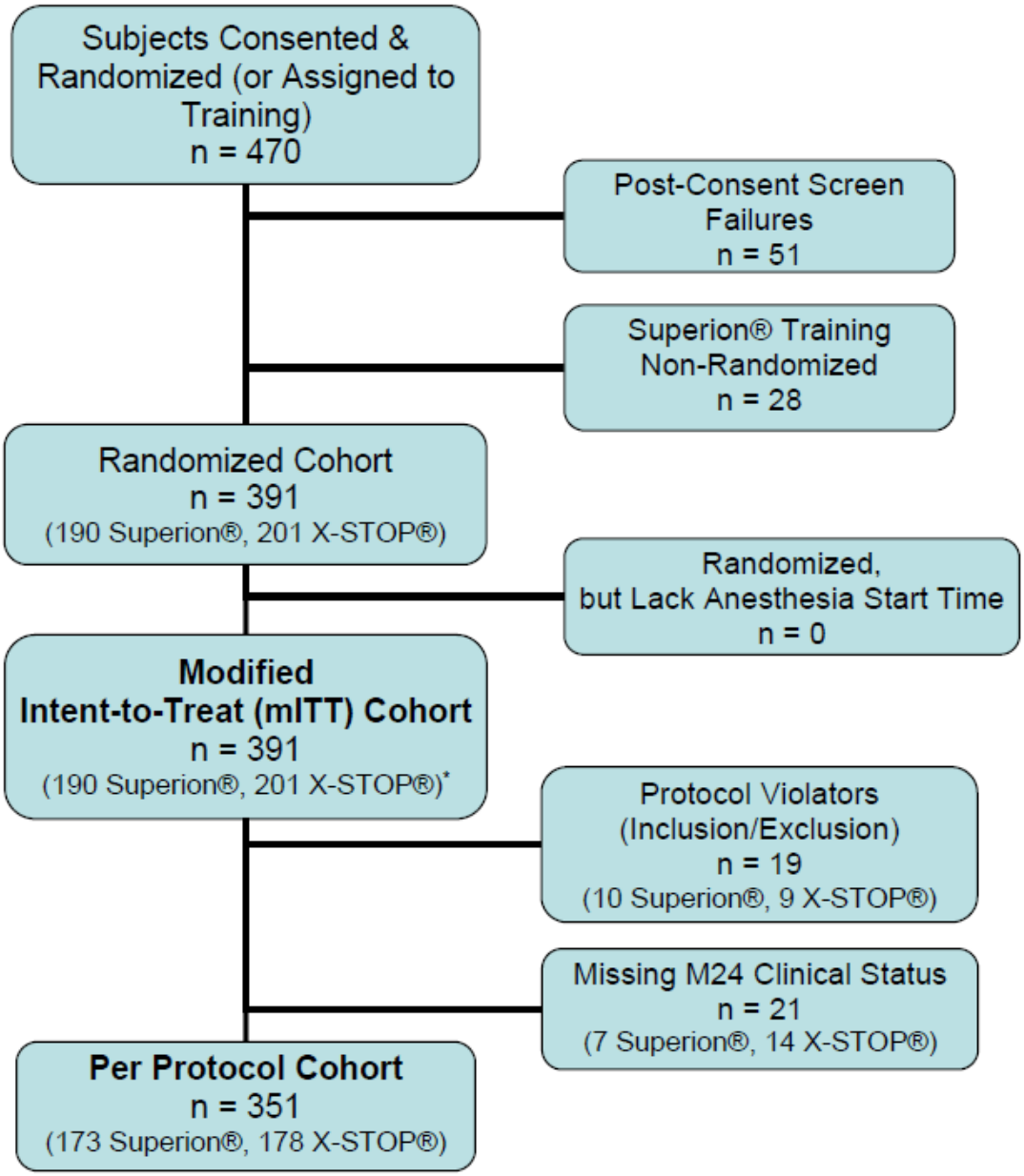
Table 2 describes the patient accounting for this clinical trial:

Table 2: Patient accounting table through July, 2014

Date of data transfer 07/07/2014	Pre-Op		Week 6		Month 3		Month 6		Month 12		Month 18		Month 24		Month 36	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(1) Theoretical follow-up	190	201	190	201	190	201	190	201	190	201	190	201	190	201	138	148
(2) Cumulative deaths	0	0	0	0	1	0	1	0	2	2	2	3	2	5	6	5
(3) Cumulative Revisions, Reoperations, and Injections	0	0	3	3	8	11	20	19	40	32	46	48	51	53	57	60
(4) Not Yet Overdue	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4
(5) Deaths+term failures among theoretical due	0	0	3	3	9	11	21	19	42	34	48	51	53	57	42	54
(6) Expected due for clinic visit	190	201	187	198	181	190	169	182	148	167	142	150	137	144	95	90
(7) Failures among theoretical due	0	0	3	3	8	11	20	19	40	32	46	48	51	53	38	50
(8) Expected due+failures among theoretical due	190	201	190	201	189	201	189	201	188	199	188	198	188	197	133	140
All Evaluated Accounting (Actual[B]) Among Expected Due Procedures																
(9) # of procedures with any clinical data in interval	190	201	182	193	171	182	164	177	145	162	132	137	131	133	81	75
(10) All Evaluated Visit Compliance (%)	100%	100%	97.3%	97%	94.5%	95.8%	97.0%	97.3%	98.0%	97.0%	93.0%	91.3%	95.6%	92.4%	85.3%	83.3%
(11) ZCQ Responder status determined	190	201	181	193	171	182	164	177	145	162	132	137	131	133	81	75
(12) Radiographic evaluation	184	194	175	178	165	187	170	182	162	175	147	161	145	150	61	51
(13) Composite clinical success	190	201	184	196	179	193	184	197	185	195	179	187	183	187	120	128
(14) Actual[B] % Follow-up for CCS	100%	100%	96.8%	97.5%	94.5%	95.8%	97.0%	97.3%	98.0%	97.0%	93.0%	91.3%	97.3%	94.9%	90.2%	91.4%
Within Window Accounting (Actual[A]) Among Expected Due																
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(15) ZCQ Responder status determined	190	201	168	179	169	180	152	167	111	122	129	131	115	113	75	70
(16) Radiographic evaluation	184	194	162	162	162	186	154	169	123	131	138	152	127	128	56	48
(17) Composite clinical success	190	201	171	182	177	191	172	186	151	154	175	179	166	166	113	120
(18) Actual[A]% Follow-up for CCS	100%	100%	89.8%	90.4%	93.4%	94.7%	89.9%	91.8%	75.0%	73.1%	90.8%	87.3%	88.3%	84.3%	85.0%	85.7%

Patient Flow

Figure 3 is the patient accounting tree which describes the flow of subjects in this clinical trial following randomization:



*There were no subjects with misallocations of randomization, meaning all patients received the device to which they were randomized. As such, the mITT cohort is identical to the "As-Treated" patient cohort.

Figure 3: Patient accounting tree

Among the 391 randomized subjects, 190 were assigned to the Superion® investigational arm, and 201 to the X-STOP® control arm. Overall, there have been 67 secondary procedures among randomized subjects during the follow-up period (38 Superion® subjects and 29 X-STOP® subjects). These constitute failures according to the approved primary endpoint, and prevented these subjects from reaching the 24-month follow-up endpoint. These failures included explantation of the device(s), with or without decompression and/or decompression and fusion, revision surgery at the index level without explantation of the device (e.g., to treat facet or synovial cyst, epidural abscess, disc protrusion), rhizotomy, and rehospitalization for treatment of deep infection. This constitutes a 17.1% secondary surgery rate among randomized subjects. Add to this the number of subjects having lumbar injections at the index level(s) (25 Superion® subjects, 13.2%; 33 X-STOP® subjects, 16.4%, nominal p = 0.395) – whether epidural steroid injections or selective nerve blocks – and there are 51 "terminal failures" in the Superion® arm at 24 months, and 53 "terminal failures" in the X-STOP® arm. Note that there were several subjects who underwent a secondary surgery, as well as received lumbar injections. These subjects were only counted as singular "terminal failures."

Additionally, a total of 21 subjects (7 Superion® subjects and 14 X-STOP® subjects) failed to reach the 24-month follow-up visit due to death, withdrawal of consent, or loss to follow-up. This constitutes a 5.4% loss rate. The actual percentage of subjects within the Superion® arm at 24 months who are evaluable for composite clinical success calculation (i.e., those with data at 24 months as a percentage of those expected at 24 months + "terminal failures") is 97.3%. For comparison, the rate in the X-STOP® control arm was 94.9%.

Operative Details

Tables 3 and 4 describe the operative details of the subjects treated in this clinical trial.

Table 3: Summary of Operative Details for Efficacy Evaluable (mITT) Cohorts

	Superion®		X-STOP®	
	n	%	n	%
Number of Subjects Treated	189		199	
Subjects Attempted / Not Implanted	1	8.4	2	3.7
Number of Levels Treated	n	%	n	%
1	99	52.4	99	49.7
2	90	47.6	100	50.3
One Level Treated	n	%	n	%
L1-L2	1	1.0	0	0.0
L2-L3	0	0.0	5	5.1
L3-L4	7	7.1	9	9.1
L4-L5	91	91.9	85	85.9
Two Levels Treated	n	%	n	%
L1-L2/L2-L3	2	2.2	1	1.0
L2-L3/L3-L4	8	8.9	7	7.0
L2-L3/L4-L5	0	0.0	1	1.0
L3-L4/L4-L5	80	88.9	91	91.0
L4-L5/L5-S1	0	0.0	0	0.0
Anesthesia Type (all patients)	n	%	n	%
General	156	82.1	179	89.1
Conscious IV Sedation	25	13.2	18	9.0
Local	14	7.4	11	5.5
Surgical Approach (as treated patients by level)	n	%	n	%
Percutaneous	131	46.8	0	0.0
Mini-Open	149	53.2	0	0.0
Open	0	0.0	299	100.0
Device Size (as treated patients by level)	n	%	n	%
6 mm (X-STOP® IPD® only)			2	0.7
8 mm	2	0.7	9	3.0
10 mm	36	12.9	71	23.8
12 mm	95	33.9	131	43.8
14 mm	117	41.8	79	26.4
16 mm (Superion™)	30	10.7	7	2.3
SupraSpinous Ligament sutured? (AT by level)	n	%	n	%
Yes	130	46.4		
No	150	53.6		
Additional procedures (as treated patients by level)	n	%	n	%
Any additional procedures	11	3.9	16	5.4
Facet(s) debulking	0	0.0	2	0.7
Osteophyte removal	3	1.1	3	1.0
Soft tissue removal	6	2.1	13	4.4
Laminectomy/wide decompression	0	0.0	1	0.3
Other	2	0.7	1	0.3

Table 4: Summary of Operative Details for Efficacy Evaluable (mITT) Cohorts

	Superion®						X-STOP®						p[1]	Effect	95% CI	
1- and 2-level procedure	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**		**Size**	**LB**	**UB**
Estimated blood loss (cc)	190	13.5	15.9	5	0	100	200	38.7	43.8	25	0	300	0.000	-0.76	-0.96	-0.55
Hospital LOS (days)	190	1.8	1.5	1	1	11	200	1.9	1.5	2	1	10	0.046	-0.11	-0.31	0.09
Operative time (minutes)	190	56.2	26.7	52	12	193	201	47.2	18.8	43	10	110	0.001	0.39	0.19	0.59
1-level procedures																
Estimated blood loss (cc)	100	9.6	12.8	5	0	70	99	29.0	30.1	20	0	200	0.000	-0.84	-1.13	-0.55
Hospital LOS (days)	100	1.6	1.2	1	1	11	99	1.9	1.5	2	1	10	0.085	-0.21	-0.49	0.07
Operative time (minutes)	100	45.1	22.1	42	12	193	100	42.0	18.1	38	10	110	0.242	0.15	-0.13	0.43
2-level procedures																
Estimated blood loss (cc)	90	17.7	17.8	10	0	100	101	48.2	52.3	30	5	300	0.000	-0.76	-1.06	-0.47
Hospital LOS (days)	90	1.9	1.7	2	1	11	101	2.0	1.5	2	1	10	0.300	-0.02	-0.30	0.27
Operative time (minutes)	90	68.6	26.0	61	30	176	101	52.4	18.2	51	20	104	0.000	0.73	0.44	1.02

Notes: [1] Wilcoxon rank sum tests for interval variables and ordinal variables.

Patient Demographics and Baseline Status

The baseline and demographic continuous variables are summarized in Tables 5 and 6 below for the Superion® ISS and X-STOP® subjects enrolled in the pivotal arm. The data demonstrates the two arms have nearly identical demographics. There was one statistically notable difference in baseline ZCQ – Physical Function, where the X-STOP® arm had a 0.1 difference more than the Superion® ISS arm. There were also several instances where the baseline demographics were trending toward a statistically notable difference (overall height, overall weight, female height). The sponsor postulates that the lower height and weight in the Superion® investigational arm can be attributed to enrolling more females, who are generally smaller in stature than males, than the X-STOP® control arm.

Table 5: Summary of Baseline and Demographic Variables for Efficacy Evaluable (mITT) Cohorts

	Superion®						X-STOP®						p	p[1]	Effect
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			**Size**
Age at surgery (yrs)	190	66.9	9.4	67.0	47.0	88.0	201	66.2	10.2	65.0	46.0	89.0	0.522	0.291	0.06
Height (inches)	190	67.2	4.2	66.9	57.1	76.0	201	67.9	3.8	68.1	59.1	77.2	0.055	0.088	-0.19
Weight (lbs)	190	189.7	36.5	189.9	89.1	288.8	201	195.8	36.9	195.5	114.9	284.4	0.099	0.105	-0.17
BMI (k/m^2)	190	29.5	4.6	29.0	16.4	40.0	201	29.7	4.6	29.4	19.8	39.5	0.609	0.667	-0.05
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Age at surgery (yrs)	110	68.0	9.0	68.0	47.0	88.0	129	66.4	10.2	66.0	46.0	87.0	0.220	0.206	0.16
Height (inches)	110	69.9	2.6	70.1	61.8	76.0	129	70.0	2.8	70.5	63.0	77.2	0.703	0.560	-0.05
Weight (lbs)	110	204.9	32.6	201.5	140.0	288.8	129	207.2	32.0	200.0	136.7	284.4	0.573	0.652	-0.07
BMI (k/m^2)	110	29.5	4.3	28.9	20.8	39.9	129	29.7	4.0	29.4	21.7	39.4	0.713	0.710	-0.05
Demographic - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Age at surgery (yrs)	80	65.3	9.7	64.5	47.0	86.0	72	65.8	10.3	64.0	47.0	89.0	0.747	0.858	-0.05
Height (inches)	80	63.4	2.8	63.0	57.1	76.0	72	64.2	2.5	64.2	59.1	70.1	0.063	0.019	-0.30
Weight (lbs)	80	168.8	31.0	169.5	89.1	238.1	72	175.4	36.3	170.4	114.9	257.9	0.228	0.288	-0.20
BMI (k/m^2)	80	29.5	5.0	29.2	16.4	40.0	72	29.8	5.4	29.3	19.8	39.5	0.721	0.788	-0.06
Baseline Functional Status	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Oswestry (ODI)	190	39.1	13.4	38.0	8.9	74.0	201	39.9	11.6	40.0	6.7	80.0	0.520	0.477	-0.06
Zurich Claudication Qx Severity	190	3.33	0.64	3.30	1.6	5.0	201	3.37	0.61	3.4	2.0	5.0	0.516	0.489	-0.07
Zurich Claudication Qx Physical	190	2.63	0.43	2.60	1.6	3.6	201	2.72	0.43	2.8	1.8	3.8	0.030	0.033	-0.22
SF-12 PCS (Physical)	190	29.2	8.4	28.8	-1.0	52.4	201	28.5	6.9	28.2	12.7	55.0	0.399	0.330	0.09
SF-12 MCS (Mental Health)	190	49.7	13.2	50.3	-1.0	73.7	201	48.9	12.2	49.4	19.6	73.8	0.535	0.433	0.06
VAS Back pain	190	55.4	27.9	63.0	0.0	93.0	201	55.1	27.4	63.0	0.0	100.0	0.910	0.809	0.01
VAS Leg pain (right leg)	190	55.0	31.3	66.0	0.0	100.0	201	52.9	32.5	61.0	0.0	100.0	0.501	0.533	0.07
VAS Leg pain (left leg)	190	49.6	31.8	60.0	0.0	100.0	201	50.8	31.7	56.0	0.0	100.0	0.702	0.758	-0.04

Notes: [1] Wilcoxon rank sum tests for interval variables and ordinal variables.

Table 6: Summary of Baseline and Demographic Variables for Efficacy Evaluable (mITT) Cohorts

	Superion®		X-STOP®		p[1]
	n	%	n	%	
Number of subjects	190		201		
Males	110	57.9	129	64.2	0.214
Females	80	42.1	72	35.8	
Race	n	%	n	%	
White	177	93.2	196	97.5	0.020
Asian	0	0.0	1	0.5	
African American	8	4.2	1	0.5	
American Indian or Alaska Native	0	0.0	0	0.0	
Native Hawaiian or Other Pacific Islander	0	0.0	1	0.5	
Other	5	2.6	2	1.0	
Ethnicity	n	%	n	%	
Hispanic or Latino	5	2.6	11	5.5	0.204
Not Hispanic or Latino	185	97.4	190	94.5	
Use of nicotine products	n	%	n	%	
No	89	46.8	101	50.2	0.809
Current Use	24	12.6	24	11.9	.
Previous Use	77	40.5	76	37.8	.

Note: [1] Fisher's exact test (2-sided).

Protocol Deviations

Major protocol deviations were defined as violations of inclusion and/or exclusion criteria, and informed consent violations. The informed consent violations included signing an incorrect consent version, or being registered (but not treated) before signing the consent. Minor violations included visits outside of window, and incomplete follow-up (e.g., partial completion of questionnaire).

When developing the per protocol patient cohort, subjects who had major protocol deviations consisting of inclusion and/or exclusion violations that did not have a sponsor waiver were excluded from the per protocol patient cohort. The primary reason for sponsor waivers was the lack of imaging studies within 3 months of the index procedure, although evidence of spinal stenosis from prior to 3 months was present with significant spinal stenosis symptoms present in these subjects.

Among randomized subjects, there were a total of 34 inclusion/exclusion violations and 5 consent violations among 33 subjects. Five (5) additional minor violations, wherein subjects at later follow-ups were not re-consented on a later revision of the consent form also occurred. These violations were corrected at the next follow-up visit. While no statistical exploratory analyses were performed assessing differences between the two groups, from the listing of protocol deviations there appeared to be no large differences in either the number of deviations or the type of deviation which occurred. Additionally, the total number of deviations which occurred for a study of this size was not concerning.

SAFETY EVALUATION

Background

Definitions

An Adverse Event (AE) was defined as any undesired clinical response or complication experienced by a subject. All operative and postoperative AEs, whether device-related or not, were recorded on the AE Case Report Forms.

The following definitions were used to determine the severity of the AE and the relationship to the device and/or procedure:

- Not related: The AE is clearly not related
- Unknown/Undetermined: The AE is unknown or undetermined to be related
- Related: The AE is clearly related
    - Device related: The AE is related to the study device or the control device
    - Procedure related: The AE is related to the procedure to implant the study or control device
    - Adjacent Level-related: The AE is related to the level(s) adjacent to the implanted study device or control device

Adjacent Level-Related AEs: In the event that an investigator indicated that an adverse event was related to a level adjacent to that at which the control or investigational device was implanted, and with concurrence by the Clinical Events Committee (CEC), radiographic assessment of that adjacent level was performed in accordance with the Radiographic Evaluation Protocol, and the data derived was compared to post-operative measurements of that level.

The severity of an AE was categorized as mild, moderate or severe. Severity was determined by the Clinical Investigator, using the following definitions, and was not necessarily the subject's interpretation:

"Mild: The AE is transient or causes mild discomfort. There usually is no intervention/therapy required and the AE does not interfere with the subject's normal activities.

Moderate: The AE causes some limitation in activity and some assistance may be needed. There is no or minimal medical intervention/therapy required.

Severe: The AE causes marked limitation in activity. The subject's usual daily activity is interrupted. The subject may require medical intervention/therapy, hospitalization is possible."

An AE was regarded as a Serious Adverse Event (SAE) if the injury or illness:

A. Resulted in death,
B. Was life-threatening,
C. Resulted in or prolongs hospitalization,
D. Resulted in permanent impairment of a body function or permanent damage to a body structure, or

E. Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Role of the Clinical Events Committee (CEC)

Per the IDE protocol, "Adverse events will be evaluated by the Medical Monitor. Data will be evaluated for safety endpoints by an independent Clinical Events Committee (CEC). The CEC will have predetermined stopping rules, one of which will be greater than 10% postoperative observation of in situ study device unlocking with full or partial collapse of the cam lobes…at annual review. The first stopping review will occur after a minimum of 30 subjects in the study group have been accrued. This observation will be monitored annually throughout the study. Additionally, safety outcomes will be determined by evaluating the type, frequency, severity, and relationship to device of adverse events through the 24-month time point for all subjects. Adverse events will be categorized as implant-related, procedure-related, adjacent level-related, or systemic. All device-related events, major procedure-related, and adjacent level-related events and therapeutic failures reported by the site PIs will be adjudicated by the independent CEC. In addition, events reported as having unknown or undetermined relationship to the device by the site PI will be adjudicated by the CEC."

Adverse Events

Overall Adverse Events

The safety profile of the Superion® device is similar to the X-STOP® device when considering adverse event incidence. The overall incidence of any adverse event (Superion® ISS: 94.7% vs. X-STOP®: 91.5%) and incidence of a serious adverse event (Superion® ISS: 46.3% vs. X-STOP®: 45.8%) were similar between both groups, as shown in Tables 7 and 8. Regarding specific adverse events, the most common adverse events observed in the Superion® ISS group and X-STOP® group were back pain, leg pain, buttock or groin pain, persistent spinal stenosis symptoms at index level, and spinous process fracture (Table 9).

Table 7: Comparisons of Summary Adverse Event Rates between Superion® and X-STOP® ITT Analysis Sets

	Superion® (I) (N=190)		X-STOP® (C) (N=201)		I vs. C		
	n	%	n	%	Diff	LB	UB
Any adverse event (per patient)	180	94.7	184	91.5	-3.2	-13.1	6.8
Any device related AE	22	11.6	15	7.5	-4.1	-14.0	5.8
Any procedure related AE	27	14.2	32	15.9	1.7	-8.2	11.6
Any serious AE	88	46.3	92	45.8	-0.5	-10.5	9.4
Serious AE that is either device or procedure related	16	8.4	19	9.5	1.0	-8.9	10.9
Deaths	6	3.2	5	2.5	-0.7	-10.6	9.3

Notes:
[1] Exact 95% confidence interval for the group difference.

Table 8: Comparisons of Summary Adverse Event Rates between Superion® and X-STOP® ITT Analysis Sets. Note that "Device Related" and "Procedure Related" adverse events include unknown and undetermined events.

	Superion® (I) (N=190)		X-STOP® (C) (N=201)		I vs. C		
	n	%	n	%	Diff	LB	UB
Any adverse event (per patient)	180	94.7	184	91.5	-3.2	-13.1	6.8
Any device related AE[2]	73	38.4	79	39.3	0.9	-9.0	10.8
Any procedure related AE[2]	72	37.9	99	49.3	11.4	1.4	21.1
Any serious AE	88	46.3	92	45.8	-0.5	-10.5	9.4
Serious AE that is either device or procedure related	40	21.1	47	23.4	2.3	-7.6	12.2
Deaths	6	3.2	5	2.5	-0.7	-10.6	9.3

Notes:
[1] Exact 95% confidence interval for the group difference.
[2] Includes "Yes" and "Unknown/Undetermined" relationships

As shown in the detailed overall adverse event table (Table 9), pain-related adverse events were distributed differently between the Superion® ISS and X-STOP® groups. X-STOP® subjects were more likely to have back pain or leg pain adverse events, while Superion® ISS subjects were more likely to have buttock or groin pain adverse events. Overall, X-STOP® subjects were more likely to have a back, leg, buttock, or groin adverse event compared with Superion® ISS subjects. In addition, X-STOP® subjects were more likely to have events related to soft tissue damage or fever. In contrast, Superion® ISS subjects were more likely to have an adverse event related to spinous process fracture.

Table 9: Counts and Percentages of Subjects with Specific Adverse Events in Superion® and X-STOP® ITT Analysis Sets

Adverse Event Type	Superion® (I) (N=190)			X-STOP® (C) (N=201)			I vs C		
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
Abdominal pain	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Allergic reaction	4	4	2.1	6	6	3.0	0.9	-9.0	10.8
Anemia	4	3	1.6	1	1	0.5	-1.1	-11.0	8.8
Angina	3	3	1.6	0	0	0.0	-1.6	-11.5	8.3
Back pain	56	50	26.3	71	66	32.8	6.5	-3.4	16.4
Bronchitis	2	2	1.1	6	5	2.5	1.4	-8.5	11.3
Cerebrovascular accident (CVA)	2	2	1.1	1	1	0.5	-0.6	-10.5	9.4
Coronary episode, ischemic	3	2	1.1	5	2	1.0	-0.1	-10.0	9.9
Deep infection at the operative site	0	0	0.0	3	2	1.0	1.0	-8.9	10.9
Deep vein thrombosis	2	2	1.1	1	1	0.5	-0.6	-10.5	9.4
Device deformation preventing device placement	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Diabetes mellitus	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Diabetes mellitus inadequate control	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Dizziness	5	5	2.6	0	0	0.0	-2.6	-12.5	7.3
Dural leaks	6	6	3.2	3	3	1.5	-1.7	-11.6	8.3
Dyspnea	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Edema	2	2	1.1	4	4	2.0	0.9	-9.0	10.8
Fever	0	0	0.0	4	4	2.0	2.0	-7.9	11.9
Gallstones	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Gastroesophageal reflux disease (GERD)	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Gastrointestinal (GI) bleed	2	2	1.1	1	1	0.5	-0.6	-10.5	9.4
Headache	1	1	0.5	5	5	2.5	2.0	-7.9	11.9
Hematoma	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Infection	15	14	7.4	17	16	8.0	0.6	-9.3	10.5
Injury, Accidental	20	15	7.9	22	19	9.5	1.6	-8.4	11.4
Leg pain	41	37	19.5	54	47	23.4	3.9	-6.0	13.8
Loss of bladder control	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Muscle damage	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Myocardial Infarction	5	5	2.6	3	3	1.5	-1.1	-11.0	8.8
Nausea	0	0	0.0	4	4	2.0	2.0	-7.9	11.9
Neurological disorder	27	22	11.6	13	13	6.5	-5.1	-15.0	4.8
Pain - buttock or groin	23	21	11.1	13	13	6.5	-4.6	-14.5	5.3
Pneumonia	5	4	2.1	5	5	2.5	0.4	-9.5	10.3
Presence of osteophyte formation associated with severe disc or facet degeneration	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Pulmonary edema	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Pulmonary embolism	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Renal failure	3	3	1.6	1	1	0.5	-1.1	-11.0	8.8
Renal insufficiency	2	2	1.1	2	2	1.0	-0.1	-10.0	9.9
Respiratory disorder	4	3	1.6	4	4	2.0	0.4	-9.5	10.3
Respiratory distress	2	2	1.1	0	0	0.0	-1.1	-11.0	8.9
Respiratory infection	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Rheumatoid arthritis	1	1	0.5	0	0	0.0	-0.5	-10.4	9.4
Sensory loss	3	2	1.1	4	4	2.0	0.9	-9.0	10.8
Shortness of breath	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Soft tissue damage	1	1	0.5	7	7	3.5	3.0	-7.0	12.9
Spinal stenosis symptoms at index level	37	35	18.4	38	34	16.9	-1.5	-11.4	8.4
Spinous process fracture	24	22	11.6	14	13	6.5	-5.1	-15.0	4.8
Stroke	1	1	0.5	1	1	0.5	0.0	-9.9	9.9
Syncope	0	0	0.0	2	2	1.0	1.0	-8.9	10.9
Transient ischemic attack (TIA)	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Urinary tract infection	8	7	3.7	6	6	3.0	-0.7	-10.6	9.2
Vertebral compression fractures	1	1	0.5	3	3	1.5	1.0	-8.9	10.9
Wound dehiscence or delayed healing	0	0	0.0	1	1	0.5	0.5	-9.4	10.4
Wound drainage	1	1	0.5	4	4	2.0	1.5	-8.4	11.4
Other, specify	15	14	7.4	10	5	2.5	-4.9	-14.8	5.1

Device Related Adverse Events

The most frequent device-related adverse events were spinous process fractures, as noted in Table 10 below, which occurred in 7.9% of Superion® subjects and 2.5% of X-STOP® subjects. Other device-related adverse events included device subsidence, device migration, device dislodgement, device breakage, device deformation, back or leg pain, spinal stenosis symptoms at the index level, dural leakage, loss of bowel control, and deep infection.

Table 10: Counts and Percentages of Subjects with Specific ***Device Related*** Adverse Events in Superion® and X-STOP® ITT Analysis Sets

	Superion® (I) (N=190)			X-STOP® (C) (N=201)			I vs C
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**p-value**
Back pain	1	1	0.5	0	0	0.0	0.486
Deep infection at the operative site	0	0	0.0	2	1	0.5	1.000
Device deformation preventing device placement	1	1	0.5	0	0	0.0	0.486
Dural leaks	1	1	0.5	0	0	0.0	0.486
Leg pain	1	1	0.5	0	0	0.0	0.486
Spinal stenosis symptoms at index level	0	0	0.0	3	3	1.5	0.249
Spinous process fracture	16	15	7.9	5	5	2.5	0.020
	Superion® (I) (N=190)			**X-STOP® (C) (N=201)**			**I vs C**
Adverse Event Type	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**p-value**
Device Dislodgement	1	1	0.5	2	2	1.0	1.000
Device Migration	1	1	0.5	5	5	2.5	0.216
Device Subsidence	4	4	2.1	0	0	0.0	0.055
Device Breakage	0	0	0.0	1	1	0.5	1.000
Loss of bowel control	0	0	0.0	1	1	0.5	1.000

Procedure Related Adverse Events

The most frequent procedure-related adverse events, as noted in Table 11 below, were spinous process fractures, which occurred in 8.9% of Superion® subjects and 3.5% of X-STOP® subjects. Other procedure-related adverse events included device subsidence, device migration, device dislodgement, device deformation, back or leg pain, spinal stenosis symptoms at the index level, dural leakage, genitourinary adverse events, and deep infection. There were no statistically notable differences in procedure-related adverse events, with the exception of spinous process fractures (Superion® ISS: 8.9% vs. X-STOP®: 3.5%, nominal p = 0.034).

Table 11: Counts and Percentages of Subjects with Specific ***Procedure Related*** Adverse Events in Superion® and X-STOP® ITT Analysis Sets

Adverse Event Type	Superion® (I) (N=190)			X-STOP® (C) (N=201)			I vs C
	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	p-value
Back pain	1	1	0.5	1	1	0.5	1.000
Coronary episode, ischemic	0	0	0.0	4	1	0.5	1.000
Deep infection at the operative site	0	0	0.0	3	2	1.0	0.499
Device deformation preventing device placement	1	1	0.5	0	0	0.0	0.486
Dural leaks	3	3	1.6	0	0	0.0	0.114
Fever	0	0	0.0	1	1	0.5	1.000
Hematoma	0	0	0.0	1	1	0.5	1.000
Infection	2	2	1.1	2	1	0.5	0.614
Leg pain	1	1	0.5	0	0	0.0	0.486
Nausea	0	0	0.0	1	1	0.5	1.000
Neurological disorder	0	0	0.0	1	1	0.5	1.000
Renal insufficiency	0	0	0.0	1	1	0.5	1.000
Respiratory disorder	0	0	0.0	2	2	1.0	0.499
Spinal stenosis symptoms at index level	0	0	0.0	3	3	1.5	0.249
Spinous process fracture	18	17	8.9	7	7	3.5	0.034
Wound drainage	0	0	0.0	4	4	2.0	0.124
Device Dislodgement	1	1	0.5	1	1	0.5	1.000
Device Migration	1	1	0.5	4	4	2.0	0.373
Device Subsidence	2	2	1.1	0	0	0.0	0.235
Genitourinary	1	1	0.5	2	2	1.0	1.000
Skin and Subcutaneous Tissue	0	0	0.0	2	2	1.0	0.499
Nausea	0	0	0.0	1	1	0.5	1.000

As noted in Tables 10 and 11 above, the adverse events following Clinical Events Committee (CEC) review, demonstrated that the Superion® ISS subjects experienced more device related adverse events (Superion®, 11.6%; X-STOP®, 7.5%), while X-STOP® subjects experienced more procedure-related adverse events (Superion, 14.2%; X-STOP®, 15.9%).

The most common device-related or procedure-related adverse event reported in the study is spinous process fracture. It should be noted that the study demonstrates a discrepancy between spinous process fractures as determined by the investigators (Superion®, 13 events in 11 subjects; X-STOP®, 10 events in 9 subjects), by the core radiology lab (Superion®, 31 events in 31 subjects; X-STOP®, 17 events in 17 subjects), and by the Clinical Events Committee (CEC) (Superion®, 24 events in 22 subjects; X-STOP®, 14 events in 13 subjects). The CEC adjudicated adverse events were used in the final adverse event analysis and are shown in Table 12 below. The sponsor has explained this discrepancy between their observations and the observations by the investigators by stating that the core radiographic lab was equipped with more sensitive equipment and some of the fractures were asymptomatic. The sponsor has provided an analysis of ZCQ, ODI, and VAS (Leg and Back) scores at 24 months in support of this statement (see Table 17 below). The core laboratory determined that 21 (67.7%) Superion® cohort fractures and 10 (58.8%) X-STOP® cohort fractures remained unhealed at 24 months.

Table 12: Spinous Process Fracture Events in Superion® IDE.

Number of Spinous Process Fractures According to Reporting Method	Training Cohort		Superion® mITT Cohort		X-STOP® mITT Cohort	
	Events	Subjects	Events	Subjects	Events	Subjects
Site Reported*	0	0	13	11	10	9
CEC Adjudicated**	3	3	24	22	14	13
Independent Radiographic Review	6	6	31	31	17	17
Non-Healed Fractures (M24)***	2	2	21	21	10	10

* Site reported fractures are those adverse events originally placed in the "spinous process fracture" category by the investigators.
**Note that the CEC had access to the results of the independent radiographic review as reported by the Radiology Core Laboratory and re-categorized several adverse events as spinous process fractures.
*** Incidences of non-healed fractures at 24 months post index procedure as determined by the Radiology Core Laboratory.

Reoperations and/or Revisions

In an effort to compare the reoperation and revision events at the index level experienced between cohorts, the sponsor provided a brief summary as shown below in Table 13. The clear majority of reoperations and revisions were performed for pain adverse events (back pain, leg pain, or combined back and leg pain).

Through 24 months, there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revisions in the X-STOP® group (29/201, 14.4%, nominal p = 0.179). Beyond 24 months, there were a total of 49 reoperations or revisions in the Superion® group (49/190, 25.8%) compared with 44 reoperations or revisions in the X-STOP® group (44/201, 21.9%, nominal p = 0.365) through the last available follow-up.

Table 13: Reoperation and Revision Events at the index level in the Superion® IDE – mITT Population

Reoperation or Revision Type	Treatment Group	Event Time Course (months)								Total (events)	Reasons
		<1.5	1.5-3	3-6	6-12	12-24	24-36	36-48	48-60		
Decompression and Device Removal	Superion®	-	3	4	8	4	7	-	-	26	20 leg and/or low back pain, 2 bone-related fracture, 2 neurological decline, 1 device deployment issue, 1 facet cyst
Device Removal and Fusion	Superion®	1	-	-	4	5	3	1	-	14	10 leg and/or low back pain, 2 bone-related fracture, 1 neurological decline, 1 unknown
Device Removal	Superion®	-	-	-	1	-	-	-	-	1	1 leg and/or low back pain
Fusion (no device removal)	Superion®	-	-	-	1	1	-	-	-	2	1 leg and/or low back pain, 1 synovial cyst
Supplemental Decompression	Superion®	-	-	2	1	1	-	-	-	4	3 leg and/or low back pain, 1 synovial cyst
I&D and Device Removal	Superion®	1	-	-	-	-	-	-	-	1	1 dural tear
Intraoperative Failure	Superion®	1							-	1	1 dural tear
Decompression and Device Removal	X-STOP®	1	1	3	3	8	4	2	1	23	18 leg and/or low back pain, 3 device dislodgement, 1 neurological decline, 1 herniated disc
Device Removal and Fusion	X-STOP®	-	-	-	1	5	5	2	-	13	12 leg and/or low back pain, 1 bone-related fracture
Device Removal	X-STOP®	-	-	-	1	-	1	-	-	2	1 leg and/or low back pain, 1 bone-related fracture
Device Replacement	X-STOP®	-	1	-	1	-	-	-	-	2	2 leg and/or low back pain
Intraoperative Failure	X-STOP®	2	-	-	-	-	-	-	-	2	2 bone-related fracture
Irrigation and Debridement	X-STOP®	2	-	-	-	-	-	-	-	2	2 deep infection

Radiographic Results

As part of the Superion® ISS clinical trial, independent review of all radiographic images was performed by Medical Metrics, Inc. This independent review utilized both qualitative and quantitative measurements performed by radiologists from a core radiographic laboratory. All radiographs were reviewed for spinous process fracture, device migration, and device dislodgement by radiologists specifically trained in review of interspinous devices using strict, *a priori* defined criteria for each of these qualitative measurements. Incidence of the radiographic observations in both the Superion® and X-STOP® treatment groups are detailed in Tables 14 and 15 below.

Table 14: Qualitative radiographic summary – Percentages over time

Measure	Device	Post-Op	6W	3M	6M	12M	18M	24M
Migrations	Superion®	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	X-STOP®	0.0%	0.0%	3.5%	4.3%	4.5%	5.0%	5.1%
Dislodgements	Superion®	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	X-STOP®	2.4%	5.1%	5.6%	5.4%	5.7%	6.6%	6.3%
Bone-Implant Interface[1]	Superion®	0.0%	1.1%	0.8%	3.9%	14.6%	19.9%	26.2%
	X-STOP®	0.0%	0.0%	1.0%	2.2%	5.3%	6.6%	10.8%
Spinous Process Fractures	Superion®	4	23	3	-	1	-	-
	X-STOP®	1	13	2	1	-	-	-

[1]Evidence of superficial bony remodeling local to the contact surface of the implant.

Table 15: Subjects with Radiographic Observations in the Superion® IDE

Radiographic Observation	Superion® (n=190)		X-STOP ® (n=201)	
	n	%	n	%
Spinous Process Fracture (any time)	31	16.3%	17	8.5%
Spinous Process Fracture (non-healed at 24 months)	21	11.1%	10	5.0%
Device Migration (>5mm)	0	0.0%	16	8.0%
Device Dislodgement	0	0.0%	20	10.0%
Any Radiographic Observation (any time)	31	16.3%	34*	16.9%
Any Radiographic Observation (24 months)	21	11.1%	28	13.9%

*Significant overlap was present in X-STOP® subjects having spinous process fractures, device migration, and device dislodgement.

Characterization of Spinous Process Fractures

As noted in Table 15, there were a greater number of spinous process fractures in the Superion® group as compared to the X-STOP® group. Table 16 provides further details regarding the characteristics of the spinous process fractures. The majority of fractures in the Superion® group are located in continuity with the device, while those in the X-STOP® group are located anterior to the device. Specifically, in the Superion® ISS group, a majority of the fractures (80.6%) present were coincident or in contact with the device, while in the X-STOP® group, a majority of the fractures (70.6%) were present anterior to the location of the device. This difference was strongly statistically notable (nominal p = 0.00023). Healing was observed at 24 months at a higher rate in fractures that were anterior to the device compared with those fractures coincident with the device (Table 16), although this finding was not strongly demonstrated (nominal p-value = 0.1928 - Fisher's Exact test).

Table 16: Location of Spinous Process Fractures in Superion® IDE

Device	Coincident with Device			Anterior to Device		
	n	% of Fractures	% Healed by 24M	n	% of Fractures	% Healed by 24M
Superion®[1]	25	80.6%	28.0% (7/25)	4	12.9%	50.0% (2/4)
X-STOP®	5	29.4%	20.0% (1/5)	12	70.6%	50.0% (6/12)

[1]Location of spinous process fracture information was not available for 2 Superion® subjects with fractures.

The majority of fractures in both Superion® [83.9% (26/31)] and X-STOP® [88.2% (15/17)] groups were displaced fractures. A displaced fracture was defined by the sponsor as no contact between the fragment and the remaining vertebra with at least a 2mm wide gap at some point along the fracture gap. However, the sponsor notes that healing of the displaced fractures was observed in a subset of subjects; 23.1% (6/26) in the Superion® group and 40.0% (6/15) in the X-STOP® group.

Risk Factors for Fracture – Superion® and X-STOP® Cohorts

At the Agency's request, the sponsor performed an exploratory post-hoc analysis to identify possible risk factors for spinous process fracture, device dislodgement, and device migration. The results of this analysis revealed that possible risk factors for spinous process fracture (Superion®) and migrations and or dislodgements (X-STOP®) included such patient factors as BMI and such procedure factors as device positioning. It is unclear if this analysis was exhaustive, considering that risk factors such as osteoporosis were not presented. At the same time, risk factors which were identified, such as BMI, may be relevant. The results of the sponsor's post-hoc analysis are presented in Appendix 1.

Consequences of Spinous Process Fracture, Device Migration, or Device Dislodgement

Spinous Process Fracture

When reviewing the possible clinical sequelae of spinous process fractures, device dislodgement, and/or migration events which occurred in conjunction with spinous process fractures, there were no notable differences demonstrated in ZCQ, ODI, VAS Back pain, VAS Leg pain, and SF-12. In addition, there were no notable differences in the number of subsequent surgical interventions. These results are shown in Tables 17 and 18 below.

Table 17: Comparison of clinical outcome measures between subjects with spinous process fractures and those without spinous process fractures.

24 Month Clinical Outcomes	Superion®		X-STOP®	
	Fracture	No Fracture	Fracture[1]	No Fracture
Pain				
VAS Back: ≥20mm decrease	78.3% (18/23)	64.8% (70/108)	46.2% (6/13)	70.8% (85/120)
VAS Leg (Worse): ≥20mm decrease	73.9% (17/23)	75.9% (82/108)	69.2% (9/13)	78.3% (94/120)
Back & Stenosis-Related Outcomes				
ZCQ Physical Function: ≥0.5 point decrease	73.9% (17/23)	72.2% (78/108)	76.9% (10/13)	80.8% (97/120)
ZCQ Symptom Severity: ≥0.5 point decrease	78.3% (18/23)	76.9% (83/108)	69.2% (9/13)	81.7% (98/120)
ZCQ Patient Satisfaction ≤2.5 points	73.9% (17/23)	86.1% (93/108)	84.6% (11/13)	92.5% (111/120)
ODI: ≥15 point decrease	65.2% (15/23)	63.0% (68/108)	61.5% (8/13)	67.5% (81/120)
Overall Quality of Life				
SF-12 Physical Function: Maintenance or Improvement	77.3% (17/22)	81.1% (86/106)	100.0% (13/13)	88.3% (106/120)
SF-12 Mental Health: Maintenance or Improvement	59.1% (13/22)	60.4% (64/106)	69.2% (9/13)	66.7% (80/120)

[1]Subjects in the fracture group for X-STOP® include those subjects who had an incidence of both spinous process fracture and migration and/or dislodgement.

Table 18: Incidence of additional surgical interventions in subjects with and without spinous process fractures.

Treatment Type	Superion®		X-STOP®	
	Fracture	No Fracture	Fracture	No Fracture
Reoperation or Revision	12.9% (4/31)	21.4% (34/159)	11.8% (2/17)	14.5% (27/186)
Epidural Steroid Injection or Nerve Root Block	12.9% (4/31)	13.2% (21/159)	17.6% (3/17)	16.1% (30/186)
Overall Additional Treatment*	**19.4% (6/31)**	**27.7% (44/159)**	**23.5% (4/17)**	**27.4% (51/186)**

Although subjects with fractures in the X-STOP® group similarly did not show notable differences in ZCQ, ODI, Back pain VAS, Leg pain VAS and SF-12 compared to subjects without fractures, the initial radiographic advantage of extension blockage demonstrated by X-STOP® was not preserved in subjects with a spinous process fracture. However, the clinical relevance of a treatment effect (i.e., extension blockage) of less than 1 degree, as detected on flexion-extension radiographs, is unclear (Tables 19 and 20).

Table 19: Changes from Pre-Op in Flexion Extension - Rotation (F to E) (deg) - Superion® mITT Cohort Stratified by Presence or Absence of Spinous Process Fracture (SPFx)

	SPFx						No SPFx								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Month 24	42	-0.92	3.46	-1.1	-10.1	7.0	177	-1.20	3.36	-0.7	-9.2	7.0	0.628	0.940	0.08
Month 36	24	-1.77	3.10	-0.6	-10.8	2.3	111	-1.67	3.38	-1.0	-9.6	6.8	0.895	0.110	-0.03

Table 20: Changes from Pre-Op in Flexion Extension - Rotation (F to E) (deg) – X-STOP® mITT Cohort Stratified by Presence or Absence of Spinous Process Fracture (SPFx)

	SPFx						No SPFx								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Month 24	24	0.30	4.87	-0.5	-11.5	10.6	198	-1.03	3.03	-0.6	-11.4	7.0	0.057	0.102	0.41
Month 36	16	0.15	3.29	-0.5	-6.1	8.2	116	-1.65	3.28	-1.1	-12.2	9.0	0.041	0.683	0.55

Device Migration and Dislodgement

According to the sponsor, the findings noted in Table 20 (i.e., loss of extension-blockage in X-STOP®) may be partially due to several fractures (7/17) in the X-STOP group being accompanied by migration/dislodgement. It appears that migration/dislodgement may affect clinical and radiographic outcomes. For example, VAS Back Pain at 24 months showed a difference in proportion success of 42.1% vs. 72.8% with a nominal p-value = 0.014 in comparing subjects with and without migration/dislodgement. Similarly, VAS Right Leg Pain showed a difference of 42.1% vs. 68.4% with a nominal p-value = 0.037. In addition, radiological flexion extension showed deterioration for subjects with migration/dislodgment (see Table 17 above and Table 21 below).

Table 21: Changes from Pre-Op in Flexion Extension - Rotation (F to E) (deg) – X-STOP® mITT Cohort Stratified by Presence or Absence of Migration/Dislodgement

	Migration/Dislodgement						No Migration/Dislodgement								
	At Level(s) of Implant (per level)												t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Month 24	28	0.23	4.76	-0.1	-11.5	10.6	194	-1.05	3.01	-0.7	-11.4	7.0	0.052	0.068	0.39
Month 36	16	0.29	4.41	-0.3	-9.7	9.0	116	-1.67	3.09	-1.1	-12.2	5.4	0.025	0.551	0.60

We will be asking the Panel to comment on the radiographic failures, and the spinous process fractures in particular.

We will also be asking the Panel a voting question on whether a reasonable assurance of safety has been demonstrated for the PMA device for its proposed intended use.

EFFECTIVENESS EVALUATION

Primary Effectiveness Endpoint

To meet the primary effectiveness endpoint, individual subjects were considered a success if they 1) demonstrated improvement in two of the three domains of the ZCQ (physical function, symptom severity, and patient satisfaction); 2) experienced no re-operations or revisions; 3) experienced no device or procedure related complications; and 4) required no spinal cord stimulators, rhizotomies, or epidural injections.

The sponsor has met the protocol specified primary composite endpoint with a posterior probability for non-inferiority of 0.9927 for the mITT and 0.9944 for the Per Protocol analysis cohorts in Table 22. Note that 0.958 is the pre-specified threshold to declare statistical success. This was calculated through a Bayesian model using Bayesian imputation for the missing data, assuming they were missing at random. The estimated overall success rates were 52.7% in the Superion® ISS group and 50.2% in the X-STOP® group.

Table 22: Superion® and X-STOP® mITT Cohort Descriptive Comparisons of the Percentages of Subjects Achieving the Primary Overall Success Efficacy Criterion All Evaluated

	Number and Percentage Achieving Month 24 Overall Success						Posterior Probability of Non-Inferiority[1]
	Superion®			X-STOP®			
Analysis Cohort	N	n	%	N	n	%	
mITT	183	95	52.7%	187	93	50.2%	0.9927
Per Protocol	173	92	53.2%	178	88	49.4%	0.9944

[1]As described in the SAP for the mITT cohort, missing data for the posterior probability was handled using Bayesian multiple imputation methodologies. The %'s, as well as the posterior probability reported for the Bayesian multiple imputation (MI) are based on the mean over 5000 multiple imputations. The (SD's) over multiple imputations for these estimates were 52.7% (0.6%), 50.2% (0.9%), and 0.9927 (0.0045), respectively. The reported N and n values for this row reflect only the numbers of patients with complete Month 24 CCS. All 190 Superion® and 201 X-STOP® patients were included in the primary analysis of the mITT cohort using Bayesian multiple imputation, whereas all patients with missing primary endpoint data at 24 months were excluded from the Per Protocol cohort.

Qualitatively similar results can be obtained when calculating the simple proportions of subjects with observed success over the non-missing subjects in the denominator. Specifically, these success rates were 51.9% and 49.7% in the Superion® ISS and X-STOP® groups respectively. Thus, the Bayesian and frequentist results were relatively consistent. It should be noted that, as shown in Table 23, the sponsor met the posterior probability of non-inferiority for all analyses except for “worst-case Superion®.” This count was achieved assuming all missing X-STOP® data points are successes and all missing Superion® data points are failures.

Table 23: Superion® and X-STOP® Modified Intent to Treat (mITT) Cohort – Descriptive Comparisons of the Percentages of Subjects Achieving the Primary Overall Success Efficacy Criterion Assessing Missing Data

Analysis	Number and Percentage Achieving Month 24 Overall Success						Posterior Probability of Non-Inferiority
	Superion®			X-STOP®			
	N	n	%	N	n	%	
Primary Analysis (Bayesian Multiple Imputation)[1]	183	95	**52.7%**	187	93	**50.2%**	0.9927
Last Observation Carried Forward (LOCF)	190	101	**53.2%**	201	99	**49.3%**	0.9971
Missing Data Excluded	183	95	**51.9%**	187	93	**49.7%**	0.9908
All Missing Data = Failures	190	05	**50.0%**	201	93	**46.3%**	0.9968
All Missing Data = Successes	190	102	**53.7%**	201	107	**53.2%**	0.9815
"Best Case" for Superion®	190	102	**53.7%**	201	93	**46.3%**	0.9997
"Worst Case" for Superion®	190	95	**50.0%**	201	107	**53.2%**	0.9123

[1]The %'s, as well as the posterior probability reported for the Bayesian multiple imputation (MI) are based on the mean over 5000 multiple imputations. The (SD's) over multiple imputations for these estimates were 52.7% (0.6%), 50.2% (0.9%), and 0.9927 (0.4%), respectively. The reported N and n values for this row reflect only the numbers of patients with complete Month 24 CCS. All 190 Superion® and 201 X-STOP® patients were included in the primary analysis using Bayesian multiple imputation.

Comparative analyses of subjects achieving success in individual components of the composite endpoints at 24 months are shown below in Table 24.

Table 24: Superion® and X-STOP® Control mITT Analysis Set – Descriptive Comparisons of the Percentages of Subjects Achieving CCS Component Success at 24 months

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
(1) ZCQ Responder (at least two of three ZCQ domains)	**131**	**107**	**81.7**	**133**	**116**	**87.2**	**0.237**
Improvement in physical function by ≥ 0.5 points	131	95	72.5	133	107	80.5	0.147
Improvement in symptom severity by ≥ 0.5 points	131	101	77.1	133	107	80.5	0.549
Mean satisfaction ≤ 2.5 points (1=very sat., 2=somewhat sat., 3=somewhat dis, 4=very dis.)	131	110	84.0	133	122	91.7	0.061
(2) No re-operations, revisions, removals or supplemental fixation at the index level(s)	**190**	**152**	**80.0**	**201**	**174**	**86.6**	**0.103**
(3) No major or implant procedure related complications defined as:	**190**	**164**	**86.3**	**201**	**166**	**82.6**	**0.332**
Failure from dislodgement or migration at any time	190	190	100.0	201	177	88.1	0.000
New or persistent worsened neurological deficit at the index level	150	143	95.3	157	152	96.8	0.566
Spinous process fractures at the index level(s)	190	169	88.9	201	191	95.0	0.038
Deep infection at the operative site requiring hospitalization, surgical draining, or IV antibiotics	190	190	100.0	201	199	99.0	0.499
Death or other permanent disability attributed to the device	190	190	100.0	201	201	100.0	.
(4) No clinically significant confounding treatments:	**190**	**165**	**86.8**	**201**	**167**	**83.1**	**0.325**
No epidural injections or nerve block procedures to treat spinal stenosis symptoms at the index level(s) at any time	190	165	86.8	201	168	83.6	0.395
No spinal cord stimulators or rhizotomies	190	190	100.0	201	200	99.5	1.000
Composite Clinical Success	**183**	**95**	**51.9**	**187**	**93**	**49.7**	**0.679**

Notes: [1] Fisher's Exact test; [2] Persistence was established by identifying new or worsening deficits at Month 18 that did not resolve by Month 24 including straight leg raise, muscle Strength, sensation to light touch, and sensation to pin prick.

The sponsor has provided a number of results exploring composite clinical success (CCS) stratified by binary categories of Age, Sex, Weight, Height and BMI. These analyses in general do not show results to contradict pooling, both within each treatment group and in comparing Superion® ISS to X-STOP®. There is one notable result (nominal p = 0.005) for X-STOP® subjects with height < 67.3" compared to ≥ 67.3", with shorter subjects having notably lower CCS success. Note that the sponsor states in the submission that there may be issues with the general X-STOP® shape and accommodation of the

interspinous space due to irregularities in the spinous process shapes. A similar difference was not observed in the Superion® ISS group.

Components of Primary Endpoint

A condensed version of Table 24 is shown below in Table 25. A brief discussion of the results of each of these components follows.

Table 25: Superion® and X-STOP® Control mITT Analysis Set – Descriptive Comparisons of the Percentages of Subjects Achieving CCS Component Success at 24 months

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value
ZCQ Responder (at least 2 of 3 ZCQ domains)	131	107	81.7	133	116	87.2	0.237
No re-op, removal, revision, or supplemental fixation	190	152	80.0	201	174	86.6	0.103
No major implant procedure related complications	190	164	86.3	201	166	82.6	0.332
No clinically significant confounding treatments	190	165	86.8	201	167	83.1	0.325
Composite Clinical Success	183	95	51.9	187	93	49.7	0.679

Zurich Claudication Questionnaire

For the components of Zurich Claudication Questionnaire, both treatments improved symptoms; however, the Superion® device demonstrated slightly less improvement compared to the X-STOP® as shown in Table 26. These findings were not nominally significant and, particularly in view of the large number of comparisons, it would not have been unusual for these or similar results to have occurred by chance.

Table 26: Superion® and X-STOP® mITT Analysis Sets Descriptive Statistics for the Zurich Claudication Questionnaire Change Scores

	Superion® Symptom Severity						X-STOP® Symptom Severity						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Week 6	181	-1.03	0.86	-1.00	-3.0	1.3	193	-1.17	0.81	-1.20	-3.6	0.9	0.098	0.117	0.17
Month 3	171	-1.04	0.86	-1.00	-3.1	1.0	182	-1.07	0.88	-1.10	-3.9	1.7	0.766	0.607	0.03
Month 6	164	-1.05	0.89	-1.10	-3.4	1.0	177	-1.17	0.85	-1.20	-3.9	0.9	0.204	0.213	0.14
Month 12	145	-1.14	0.88	-1.10	-3.2	0.9	162	-1.18	0.78	-1.30	-3.6	0.6	0.628	0.715	0.06
Month 18	132	-1.11	0.90	-1.20	-3.3	1.1	137	-1.18	0.94	-1.10	-3.6	1.0	0.521	0.562	0.08
Month 24	131	-1.15	0.89	-1.30	-3.1	1.4	133	-1.28	0.91	-1.30	-3.6	1.0	0.242	0.410	0.14
Month 36	82	-1.33	0.90	-1.30	-3.3	1.5	77	-1.19	0.92	-1.30	-3.6	1.0	0.322	0.370	-0.16

	Superion® Physical Function						X-STOP® Physical Function						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Week 6	181	-0.75	0.65	-0.80	-2.2	0.8	193	-0.87	0.68	-0.80	-2.4	1.0	0.064	0.055	0.19
Month 3	171	-0.78	0.66	-0.80	-2.2	1.2	182	-0.91	0.69	-1.00	-2.6	1.2	0.075	0.059	0.19
Month 6	164	-0.77	0.71	-0.80	-2.4	1.2	177	-0.99	0.68	-1.00	-2.4	0.8	0.003	0.006	0.32
Month 12	145	-0.88	0.68	-1.00	-2.4	1.0	162	-0.99	0.70	-1.00	-2.4	0.8	0.193	0.174	0.15
Month 18	132	-0.86	0.67	-1.00	-2.2	1.0	137	-1.02	0.73	-1.00	-2.4	1.0	0.071	0.098	0.22
Month 24	131	-0.89	0.71	-1.00	-2.2	1.4	133	-1.09	0.70	-1.20	-2.4	0.8	0.023	0.028	0.28
Month 36	82	-1.04	0.60	-1.00	-2.2	0.4	77	-1.05	0.64	-1.00	-2.2	0.6	0.977	0.904	0.00

Notes:

[1] Two sample pooled t-test p-value.

[2] Two sample Wilcoxon rank sum test p-value.

[3] Standardized effect size (group difference in means divided by pooled within group SD). Smaller values in the Symptom Severity and Physical Function scores reflect greater health related quality of life. Therefore, negative effect sizes reflect improved health related quality of life for subjects implanted with the investigational device relative to control.

Reoperations, Removals, Revisions, or Supplemental Fixation

For the component of "no re-ops, removals, revisions, or supplemental fixation at the index level(s)," in the modified intent-to-treat patient population, through 24 months (as part of the primary endpoint), there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revisions in the X-STOP® group (29/201, 14.4%, nominal p = 0.179).

Beyond 24 months, there were a total of 49 reoperations or revisions in the Superion® group (49/190, 25.8%) compared with 44 reoperations or revisions in the X-STOP® group (44/201, 21.9%, nominal p = 0.365) through the last available follow-up, which included time points past 24 months for many subjects. Reoperations and revisions in subjects prior to day 730 of treatment were considered to be failures in the primary endpoint although, as noted above, there was an increased number of reoperations and revisions in the X-STOP® arm, vs. the Superion® arm, at time points after 2 years.

Implant and Procedure Related Complications

For the component of dislodgement, migration or deformation, 24 of the 201 (11.9%) X-STOP® mITT subjects had a device dislodgement or migration, and none of the Superion® ISS subjects experienced this type of event (Fishers Exact nominal p-value < 0.0001). In terms of spinous process fractures that were considered CCS failures, 21 of the 190 (11.1%) Superion® ISS mITT subjects had a spinous process fracture that did not heal by Month 24. In contrast, 10 of the 201 (5.0%) X-STOP® mITT subjects had a spinous process fracture that did not heal by the 24-month time point.

The rate of neurologic failures (defined as new or worsening persistent motor or sensory neurologic assessments) was similar for both Superion® ISS and X-STOP® groups. The Superion® ISS patient population had 7 failures (3.7%), while the X-STOP® population had 5 failures (2.5%).

Clinically Significant Confounding Treatments

Following index surgery, 0 of the 190 (0.0%) Superion® ISS mITT subjects received a rhizotomy at the level(s) of surgery prior to Month 24. In contrast, 1 of the 201 (0.5%) X-STOP® mITT subjects received a rhizotomy and was therefore considered a study failure. No subject in either group received a spinal cord stimulator at the level(s) of surgery prior to Month 24. Following index surgery, 25 of the 190 (13.2%) Superion® ISS mITT subjects received an epidural steroid injection or nerve block at the level(s) of surgery prior to month 24 and were considered study failures as a result. In contrast, 33 of the 201 (16.4%) X-STOP® mITT subjects received an epidural steroid injection or nerve block at the level(s) of surgery prior to Month 24 (nominal p-value = 0.395).

Additional Stratified Outcomes

As the device was indicated for 1 or 2-Level treatments, additional analyses were performed stratifying CCS results by level implanted and number of levels. As shown in Tables 27 and 28, non-inferiority of the Superion® device was also demonstrated comparing the results of 1-Level and 2-Level procedures.

Table 27: Superion® and X-STOP® Control ITT Analysis Set (1-Level) – Descriptive Comparisons of the Percentage of Subjects Achieving Composite Clinical Success (CCS)

	Number and Percentage Meeting Criteria						
	Superion®			X-Stop®			
Date of data transfer 02/07/2014	N	n	%	N	n	%	p-value[1]
Composite Clinical Success	96	53	55.2	95	46	48.4	0.386

Notes: [1] Fisher's Exact test; [2] Persistence was established by identifying new or worsening deficits at Month 18 that did not resolve by Month 24 including straight leg raise, muscle Strength, sensation to light touch, and sensation to pin prick.

Table 28: Superion® and X-STOP® Control ITT Analysis Set (2-Level) – Descriptive Comparisons of the Percentage of Subjects Achieving Composite Clinical Success (CCS)

	Number and Percentage Meeting Criteria						
	Superion®			X-Stop®			
Date of data transfer 02/07/2014	N	n	%	N	n	%	p-value[1]
Composite Clinical Success	87	42	48.3	92	47	51.1	0.766

Notes: [1] Fisher's Exact test; [2] Persistence was established by identifying new or worsening deficits at Month 18 that did not resolve by Month 24 including straight leg raise, muscle Strength, sensation to light touch, and sensation to pin prick.

In conclusion, the Superion® ISS did somewhat worse for the ZCQ, reoperation/revision, and spinous process fracture components, but this was offset by better results in the migration/dislodgements and confounding treatments (epidurals) components of the primary endpoint at 24 months. None of the differences other than migrations/dislodgements were statistically significant.

Longer Term Outcomes

As of the date of the latest database lock of July 7, 2014, there was follow-up of 90.2% (120/133) for the Superion® device and 91.4% (128/140) for the X-STOP® control at 36 months. Note that there was a strong advantage for Superion® in composite clinical success at this time point, with success rates of 52.5% and 38.0% (p = 0.023) for the Superion® and X-STOP® groups respectively as demonstrated by Table 29 below. In addition, there was a difference in VAS Leg Pain with 84.1% of Superion® and 69.7% of X-STOP® subjects (nominal p = 0.037) having success (improvement ≥ 20mm). There were also numerical advantages for Superion® in ZCQ symptom severity and VAS Back Pain.

Table 29: Superion® and X-STOP® Control mITT Analysis Set - Descriptive Comparisons of the Percentages of Subjects Achieving Component Success at 36 Months

	Number and Percentage Meeting Criteria						
Date of data transfer 07/07/2014	**Superion®**			**X-Stop®**			
	N	**n**	**%**	**N**	**n**	**%**	**p-value[1]**
(1) ZCQ Responder (at least two of three ZCQ domains)	**81**	**71**	**87.7**	**75**	**63**	**84.0**	**0.646**
Improvement in physical function by ≥ 0.5 points	81	65	80.2	75	58	77.3	0.698
Improvement in symptom severity by ≥ 0.5 points	81	67	82.7	75	56	74.7	0.244
Mean satisfaction ≤ 2.5 points (1=very sat., 2=somewhat sat., 3=somewhat dis, 4=very dis.)	81	74	91.4	75	66	88.0	0.600
(2) No re-operations, revisions, removals or supplemental fixation at the index level(s)	**138**	**112**	**81.2**	**148**	**118**	**79.7**	**0.768**
(3) No major or implant procedure related complications defined as:	**138**	**125**	**90.6**	**148**	**126**	**85.1**	**0.206**
Failure from dislodgement or migration	138	138	100.0	148	132	89.2	0.000
New or persistent worsened neurological deficit at the index level	113	109	96.5	112	108	96.4	1.000
Spinous process fractures at the index level(s)	138	125	90.6	148	141	95.3	0.164
Deep infection at the operative site requiring hospitalization, surgical draining, or IV antibiotics	138	138	100.0	148	146	98.6	0.499
Death or other permanent disability attributed to the device	138	138	100.0	148	148	100.0	.
(4) No clinically significant confounding treatments:	**138**	**120**	**87.0**	**148**	**118**	**79.7**	**0.115**
No epidural injections or nerve block procedures to treat spinal stenosis symptoms at the index level(s)	138	120	87.0	148	119	80.4	0.152
No spinal cord stimulators or rhizotomies	138	138	100.0	148	147	99.3	1.000
Composite Clinical Success	**120**	**63**	**52.5**	**129**	**49**	**38.0**	**0.023**

Notes: [1] Fisher's Exact test;

We will be asking the Panel a voting question on whether a reasonable assurance of effectiveness has been demonstrated for the PMA device for its proposed intended use.

Secondary Outcomes

The sponsor reports on the following secondary outcomes: Oswestry Disability Index (ODI), VAS Back Pain, VAS Right Leg, VAS Left Leg, SF-12, Patient Satisfaction and various Radiographic measures.

Table 30: Superion® and X-STOP® mITT Analysis Set – Secondary Endpoint Successes at 24 months

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
Improvement of at least 15 pts in ODI	133	83	63.4	133	89	66.9	0.606
Increase of at least 20 mm on leg pain (worse) VAS	131	99	75.6	133	103	77.4	0.772
Increase of at least 20 mm on back pain VAS	131	88	67.2	133	91	68.4	0.895
Maintenance or improvement of SF-12 PCS	128	103	80.5	133	119	89.5	0.055
Maintenance or improvement of SF-12 MCS	128	77	60.2	133	89	66.9	0.303
Notes: [1]Fisher's Exact test							

Secondary outcomes for available subjects at 36 months are presented in the tables below.

Oswestry Disability Index

The ODI success rates at 24 months were 63.4% for the Superion® ISS arm and 66.9% for the X-STOP® arm with a Fisher's exact nominal p-value of 0.606. At 36 months, these numbers were 69.5% and 71.4% for the Superion® and X-STOP® groups respectively, with nominal p-value = 0.863.

Table 31: Superion® and X-STOP® mITT Analysis Set Descriptive Comparisons of the Percentages of Subjects Achieving a Decrease in Oswestry Disability Index (ODI) Score of at least 15 Points

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
Week 6	182	89	48.9%	193	108	56.0%	0.180
Month 3	171	93	54.4%	182	117	64.3%	0.065
Month 6	164	95	57.9%	177	110	62.1%	0.440
Month 12	145	85	58.6%	162	104	64.2%	0.348
Month 18	132	75	56.8%	137	94	68.6%	0.058
Month 24	131	83	63.4%	133	89	66.9%	0.606
Month 36	82	57	69.5%	77	55	71.4%	0.863
Notes: [1] Fisher's Exact test.							

VAS Back and VAS Leg Pain

For VAS Back Pain at 24 months, the success rates were 67.2% for the Superion® ISS and 68.4% for the X-STOP® arms, with a nominal p-value of 0.895. At 36 months, these numbers were 76.8% for the Superion® and 69.7% for the X-STOP with nominal p-value = 0.369. The success rates for VAS Leg at 24 months were 75.6% versus 77.4% for the Superion® ISS versus the X-STOP® with a nominal p-value of 0.772. As discussed above, at 36 months, the success rates were 84.1% for the Superion® and 69.7% for the X-STOP with nominal p-value = 0.037.

Table 32: Superion® and X-STOP® mITT Analysis Set Descriptive Comparisons of the Percentages of Subjects Achieving a Decrease in VAS Back Pain

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
Week 6	179	113	63.1%	193	124	64.2%	0.830
Month 3	169	112	66.3%	181	120	66.3%	1.000
Month 6	161	94	58.4%	177	106	59.9%	0.825
Month 12	143	90	62.9%	160	108	67.5%	0.468
Month 18	131	82	62.6%	137	91	66.4%	0.526
Month 24	131	88	67.2%	133	91	68.4%	0.895
Month 36	82	63	76.8%	76	53	69.7%	0.369

Notes: [1] Fisher's Exact test.

Table 33: Superion® and X-STOP® mITT Analysis Set Descriptive Comparisons of the Percentages of Subjects Achieving a Decrease in VAS Leg Pain

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
Week 6	179	136	76.0%	193	147	76.2%	1.000
Month 3	169	116	68.6%	181	129	71.3%	0.641
Month 6	161	106	65.8%	177	135	76.3%	0.041
Month 12	143	102	71.3%	160	121	75.6%	0.435
Month 18	131	96	73.3%	137	100	73.0%	1.000
Month 24	131	99	75.6%	133	103	77.4%	0.772
Month 36	82	69	84.1%	76	53	69.7%	0.037

Notes: [1] Fisher's Exact test.

SF-12 Survey

For the SF-12 Physical Component Summary the proportion of subjects maintaining or improving were 80.5% vs. 89.5% at 24 months (nominal p-value 0.055) and 89.0% vs. 86.6% at 36 months (nominal p-value = 0.808) for the Superion® and X-STOP® respectively. For the Mental Component Summary, these

results were 60.2% vs. 66.9% at 24 months (nominal p-value = 0.303) and 63.4% vs. 60.5% at 36 months (nominal p-value = 0.745) for the Superion® compared to the X-STOP®.

Table 34: Superion® and X-STOP® mITT Analysis Set Descriptive Comparisons of the Percentages of Subjects Maintaining or Improving SF-12 Physical Function Component HRQoL

	Number and Percentage Meeting Criteria						
	Superion®			X-STOP®			
	N	n	%	N	n	%	p-value[1]
Week 6	180	143	79.4%	193	163	84.5%	0.226
Month 3	169	140	82.8%	180	155	86.1%	0.460
Month 6	164	131	79.9%	177	153	86.4%	0.112
Month 12	143	121	84.6%	161	141	87.6%	0.507
Month 18	130	110	84.6%	137	124	90.5%	0.192
Month 24	128	103	80.5%	133	119	89.5%	0.055
Month 36	82	73	89.0%	76	66	86.8%	0.808
Notes: [1] Fisher's Exact test.							

Patient Satisfaction Survey

As shown in Table 35 below, for patient satisfaction, at earlier time points there was somewhat higher patient satisfaction with the X-STOP®, but results at 24 months were more similar between the two groups. Namely, in the Superion® ISS group 86.2% of subjects were “Satisfied” or “Somewhat Satisfied,” whereas this number was 88.5% for the X-STOP®. Also, 82.9% of Superion® ISS subjects vs. 84.1% of X-STOP® subjects answered “Definitely Yes” or “Probably Yes” to whether they would have the same treatment again. Satisfaction results at 36 months were not provided.

Table 35: Patient Satisfaction at Month 24 by Treatment Group – mITT Analysis Set

	Superion®		X-STOP®		
	n	%	n	%	p-value
How satisfied were you with your treatment?					
Satisfied	114	75.0	123	78.3	0.836
Somewhat Satisfied	17	11.2	16	10.2	0.856
Somewhat Dissatisified	0	0.0	0	0.0	1.000
Dissatisfied	21	13.8	18	11.5	0.505
	n	%	n	%	p-value
Would you have the same treatment again?					
Definitely yes	96	63.2	108	68.8	0.545
Probably yes	30	19.7	24	15.3	0.306
Probably no	14	9.2	16	10.2	0.852
Definitely yes	12	7.9	9	5.7	0.503

In conclusion, there was a trend toward slightly better effectiveness outcomes for the X-STOP® in the secondary endpoints at 24 months. However, in later follow-up (i.e., at 36 months) these trends are in general reversed and there appears to be greater effectiveness of the Superion® treatment.

Other Radiographic Measures

Radiographic assessments did not demonstrate any statistical differences in Flexion/Extension angles between the two devices. Similarly, there were no statistical differences for Translation. The sponsor reports that these devices did not create extra or reduced translation. For L1-S1 global angle, there is a statistical difference between the groups, but the clinical significance of this difference is limited to the observation that Superion® ISS subjects returned to the pre-operative value earlier than X-STOP® subjects. In terms of disc angle, the changes from the pre-operative disc angle measurements are nominally significant at every time point from post-operative through 24 months. At every time point, the changes were smaller in the Superion® ISS group. The greater differences in the X-STOP® group are consistent with other radiographic data that suggest that the larger distraction caused by the X-STOP® devices creates a levering effect that reduces the disc angle more than the Superion® ISS. However, the sponsor postulates that in both cases the devices are performing in a manner consistent with their mechanism of action (i.e., to fit between the spinous processes and block extension).

Spondylolisthesis Progression

For spondylolisthesis progression, there were no notable differences between Superion® ISS and X-STOP® at the index levels. The values suggest changes in spondylolisthesis conditions relative to pre-op were maintained to Month 24. In all cases, spondylolisthesis was slightly decreased. Anterior disc height changes from the pre-operative measurements at the index level are nominally statistically different at 6 weeks through 18 months. At each time point, the X-STOP® group had a larger decrease in anterior disc height. This difference is consistent with the observation that X-STOP® geometry leads to greater distraction. Conversely, there was a statistically greater increase in posterior disc height at all time points in the X-STOP® group. It is noteworthy that posterior disc height was slightly decreased at 24 months relative to pre-op in the Superion® ISS group. The change in spinous process distance and foraminal height relative to pre-op are statistically different between the Superion® ISS and X-STOP® groups at nearly all time points. In each case, the increase in spinous process distance and foraminal height are greater in the X-STOP® group. Again, the sponsor postulates that this is likely due to X-STOP® design and spinous process geometry.

Bone/Implant Interface Changes

Bone-Implant Interface data showed higher rates of radiographic events in the Superion® ISS group at 6 months through 24 months. These events were related to bony remodeling around the implants. The sponsor states that this radiographic observation is expected, since the Superion® ISS has less contact area with the adjacent spinous processes. As a result, the surrounding bone remodels in response to the more localized stresses. The sponsor conducted an exploratory analysis which showed Superion® ISS subjects with bone-implant interface changes had similar clinical outcomes compared to the remainder of the Superion® ISS patient population. The sponsor hypothesizes that this bony remodeling could contribute to the lack of dislodgements and migrations in the Superion® ISS group. Note also that, in both groups, there was a very low rate (< 2%) of exuberant bone formation present at 24 months.

In conclusion, the radiographic analyses demonstrated more dramatic distraction with the X-STOP® compared to the Superion® device. The sponsor postulates that this greater distraction may also be related to the higher rate of migrations and dislodgements observed in the X-STOP® group.

Effectiveness Analysis Populations

The sponsor has provided the following Per Protocol analysis:

Table 36: Superion® and X-STOP® Per Protocol Cohort Descriptive Comparisons of the Percentages of Subjects Achieving the Primary Overall Success Efficacy Criterion All Evaluated

	Number and Percentage Achieving Month 24 Overall Success						Posterior Probability of Non-Inferiority[1]
	Superion®			X-STOP®			
Analysis Cohort	N	n	%	N	n	%	
mITT	183	95	52.7%	187	93	50.2%	0.9927
Per Protocol	173	92	53.2%	178	88	49.4%	0.9944

[1]As described in the SAP for the mITT cohort, missing data for the posterior probability was handled using Bayesian multiple imputation methodologies. The %'s, as well as the posterior probability reported for the Bayesian multiple imputation (MI) are based on the mean over 5000 multiple imputations. The (SD's) over multiple imputations for these estimates were 52.7% (0.6%), 50.2% (0.9%), and 0.9927 (0.0045), respectively. The reported N and n values for this row reflect only the numbers of patients with complete Month 24 CCS. All 190 Superion® and 201 X-STOP® patients were included in the primary analysis of the mITT cohort using Bayesian multiple imputation, whereas all patients with missing primary endpoint data at 24 months were excluded from the Per Protocol cohort.

This analysis shows that non-inferiority continues to hold in the Per Protocol analysis population.

Missing Data

The sponsor states that the missing data at 24 months consists of 7 Superion® ISS and 14 X-STOP® subjects. This missing data was implicitly imputed in the Bayesian analysis of the primary endpoint through the use of Bayesian multiple imputation. Note that this imputation used only the earlier follow-up times without considering covariates. In addition the sponsor has provided the following sensitivity analyses: last-observation-carried-forward, complete-case, all-missing-as-success, all-missing-as-failure, best-case, and worst-case. All of these analyses with the exception of worst-case demonstrated non-inferiority. The sponsor also provided a tipping-point analysis, which is shown below in Figure 4.

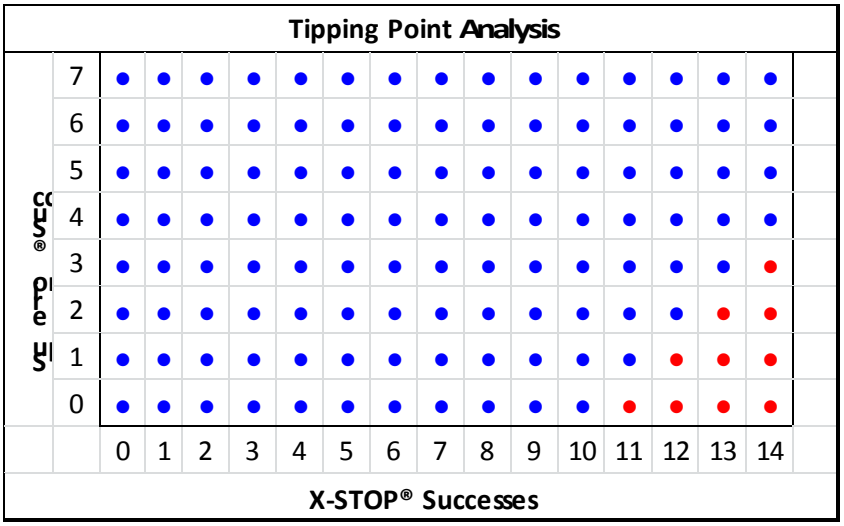


Figure 4: Tipping Point Analysis for Superion® IDE
● denotes Posterior Probability of Non-Inferiority ≥0.958,
● denotes Posterior Probability of Non-Inferiority <0.958.

This tipping point analysis shows that the non-inferiority conclusion is relatively robust to missing data as only a small proportion of the scenarios (in red) fail to show non-inferiority success. Note that tipping point analyses are particularly important because the sponsor's imputation approach to the missing data is not completely valid. Namely, the sponsor treated missing subjects as if they were incomplete. This treatment of missing subjects is not ideal, as these subjects were likely not missing at random. However, the above tipping point analysis includes both incomplete and missing subjects and demonstrates that the non-inferiority results are relatively robust to the missing data. Specifically, the scenarios where non-inferiority is not demonstrated consist of very low rates of success among missing Superion® ISS subjects and quite high rates of success among missing X-STOP® subjects. This sort of imbalance could be considered not to be very plausible. Thus, due to the relatively high follow-up rates and as demonstrated by the above tipping point results; missing data is not greatly a concern in this study.

Poolability of Sites

The data were shown to be poolable by site. Although the Breslow-Day test rejected homogeneity (nominal p-value = 0.033), the data were later found not to meet the requirements for this test. Namely,

the individual tables had too little information even after pooling the lowest enrolling sites. Specifically, 62.5% of the table cells had an expected count < 5, whereas this number is recommended to be lower than 20% for the asymptotics of the test to hold. An alternative meta-analytic approach did not find statistical heterogeneity by site with the proportion of the variation attributable to heterogeneity (designated by I^2) having a value of 24% with a nominal p-value of 0.12. Note that the sponsor argues that this value of I^2 is typically considered to be in the low range. In addition, a sensitivity analysis using a Bayesian hierarchical model found results consistent with the original analysis with a posterior probability of non-inferiority of the Superion® treatment of 0.9525.

Financial Interest

The sponsor reports that only one investigator had disclosable financial interest in the device and the VertiFlex® parent company. This investigator served in the role of consulting Medical Director for VertiFlex®.

Sources of Bias

The most important possible source of bias is observer/reporting bias. The concern of observer/reporting bias arises because study evaluators and subjects were essentially unblinded. However, concern about bias could be considered as mitigated because the study had two active treatments with little reason for subjects to prefer one device over another. In addition, note that there was almost no financial interest among investigators, as mentioned above.

Another possible source of bias was the exclusion of subjects from treatment after randomization, as appears to have been done for 51 subjects in this study. However, these subjects actually withdrew due to personal withdrawal of consent or a laboratory finding that did not fit the inclusion/exclusion criteria without knowing which treatment they had been randomized to. While the electronic data capture system generated the randomization, these were not accessible by VertiFlex® or the investigational sites.

Benefit-Risk Assessment

Summary of Benefits

Over the 24-month time period studied, the following benefits were observed with use of the VertiFlex® Superion® InterSpinous Spacer (ISS) when compared to the control device (X-STOP®):

1) Improvement in neurogenic intermittent claudication symptoms as measured by the Zurich Claudication Questionnaire (ZCQ) Score at 24 months post-operatively compared to baseline (proportion of subjects achieving protocol defined ZCQ success: Superion®, 81.7%; X-STOP®, 87.2%).
2) Functional improvement measured by the improvement in Oswestry Disability Index (ODI) scores at 24 months post-operatively compared to baseline (proportion of subjects achieving protocol defined ODI success: Superion®, 64.3%; X-STOP®, 66.9%).
3) Maintenance or improvement in neurological status at 24 months post-operatively (proportion of subjects achieving protocol defined neurologic success: Superion®, 95.3%; X-STOP®, 96.8%).
4) Despite longer operative times, less blood loss (numerically different, not statistically significant) reported during the surgical implantation of the Superion® device as compared to the control

device (mean operative time: Superion®, 56.2 minutes; X-STOP®, 47.2 minutes; estimated blood loss: Superion®, 13.5cc; X-STOP®, 38.7cc).

Summary of Risks

Over the 24 month time period studied, the following risks were identified:

1) The overall rate of adverse events with the Superion® device was comparable to the control device (Superion®, 94.7%; X-STOP®, 91.5%).
2) The rate of serious adverse events with the Superion® device was comparable to the control device (Superion®, 46.3%; X-STOP®, 45.8%).
3) The rate of serious adverse events that were either device- or procedure-related with the Superion® device was comparable to the control device (Superion®, 8.4%; X-STOP®, 9.5%).
4) The incidence of spinous process fractures observed with the Superion® device was numerically higher than those observed with the control device (Superion®, 16.3%; X-STOP®, 8.5%; as reported by the independent radiographic reviewers), and the long-term effect of these fractures on safety and effectiveness is unclear.
5) Through 24 months, there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revisions in the X-STOP® group (29/201, 14.4%).

Summary of Other Factors

1) The overall success rate for both the investigational and control cohorts is just over 50% (Superion®, 52.7%; X-STOP®, 50.2%; for the mITT population) using a composite endpoint including clinical success, lack of additional treatments for stenosis, and lack of radiographic observations at 24 months postoperatively. To date, randomized controlled trials [5, 13, 14] have not shown an advantage for the use of non-fusion interspinous process devices compared to traditional lumbar decompressive surgery in the treatment of lumbar spinal stenosis. In addition, non-fusion interspinous process devices have been associated with higher reoperation rates compared to traditional lumbar decompressive surgery for treatment of lumbar spinal stenosis at both one and two year follow-up [5, 13, 14].
2) Sensitivity analyses were conducted which supported the conclusions of this study.
3) More than half of the observed spinous process fractures in the investigational group had not healed at 24 months.
4) Concern exists with the methodology of diagnosing spinous process fractures in this study (i.e., plain radiographs). According to literature [2], plain radiography is not sufficiently sensitive for detection of spinous process fractures, and CT imaging is required to identify the vast majority of spinous process fractures in subjects implanted with interspinous process spacers, based on a single site investigation of 38 subjects.
5) Although the rate of revision surgery was not statistically different between the Superion® group and the X-STOP® group, literature has shown that interpinous process spacers are associated with higher rates of revision surgery compared to spinal decompression or spinal fusion (13-17).
6) The study population was a mixed population of spinal stenosis subjects and included subjects without spondylolisthesis, as well as subjects with up to Grade 1 degenerative spondylolisthesis. Recent literature suggests that subjects with degenerative spondylolisthesis should be considered as a distinct sub-population of spinal stenosis subjects [11]. In addition, the use of

interspinous process devices to treat subjects with degenerative spondylolisthesis is controversial [12]. The success results presented by the sponsor were similar for Superion® subjects with Grade 1 spondylolisthesis and without spondylolisthesis (57.4% vs. 48.7%, respectively, for the mITT population).

7) While the Superion® device may be implanted via a minimally invasive approach (12 – 15mm midline posterior lumbar incision), or a mini-open approach, the X-STOP® device requires implantation via an open midline posterior lumbar incision. While the sponsor proposes use of a minimally invasive surgical approach as a benefit of their device, current literature reports that the incidence rates of complications and reoperations are similar, whether interspinous process spacers are implanted by either a minimally invasive or open surgical technique [9].
8) There is an absence of data regarding patient perception of the risks and benefits of the device.
9) Risks may potentially be mitigated by the labelling of the device if the Superion® InterSpinous Spacer (ISS) is found approvable.
10) Post-approval studies will be conducted to study the long-term performance of the device.

Conclusion

The Superion® device met the primary clinical study endpoint for success. The Superion® implant resulted in a similar percentage of adverse events as the control. However, radiographic observations differ in type, with the majority of observations with the Superion® device being spinous process fractures and those of the control being migrations and dislodgements.

We will be asking the Panel a voting question on whether a favorable benefit-risk has been demonstrated for the PMA device for its proposed intended use.

POST-APPROVAL STUDY

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision, or is making a recommendation, on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has made the recommendation that if the VertiFlex® Superion® InterSpinous Spacer is approved, a post-approval study (PAS) should be required as a condition of approval. Through premarket review of the PMA, the FDA team has identified the following postmarket concerns and recommended conducting a PAS to provide the assessment of device safety and effectiveness in a longer term:

- Use of appropriate comparison group evaluation of the device performance as it compares to the current standard of care for the indication;
- Use of appropriate end-points to assess device safety and effectiveness;
- Specific adverse event assessment in a longer term, including-evaluation of the relationship between spinous process fractures and adverse events; and
- Use of appropriate diagnostic methods and procedures to accurately evaluate the rate of spinous fractures.

Overview of Proposed Post-Approval Studies

To address the identified postmarket concerns the sponsor submitted a revised PAS outlines dated October 6, 2014 (P140004/A004). An overview of the proposed PAS outlines is provided below.

<u>Study 1: Extended follow-up of premarket study (Investigating Superion® ISS in Spinal Stenosis)</u>

Objective
To assess long-term safety and effectiveness of the device by comparing the Superion® InterSpinous Spacer (ISS) to the X-STOP® Interspinous Process Decompression (IPD®) System in Subjects with Moderate Lumbar Spinal Stenosis.

Study Design and Population
This is multicenter follow up of both arms of the RCT IDE study. The proposed PAS will involve longitudinal prospective evaluation of study subjects participating in all study arms of the pivotal IDE who were not determined to be failures during IDE stage (136 Superion® mITT subjects and 143 X-STOP® mITT subjects). Subjects suffering from moderate symptoms of neurogenic claudication secondary to a confirmed diagnosis of LSS at one or two contiguous levels from L1 to L5 who met all inclusion/exclusion criteria were enrolled in IDE study.

Hypothesis
The primary hypothesis is that the clinical performance of the Superion® ISS is noninferior to the clinical performance achieved with the active control, X-STOP® IPD®.

Enrollment Plan and Follow-up
The sponsor proposes that all subjects who did not fail (see the composite success criteria) during the IDE stage will be enrolled in the PAS and followed annually through the 5th year.

The proposed annual follow-up for 5 years may provide the evaluation of long-term safety and effectiveness of the Superion® InterSpinous Spacer. Under IDE protocol, subjects are consented for up to 10 years. Because there is limited data on long-term performance for both Superion® and X-STOP® the FDA believes that a follow-up period of 5 years of the IDE subjects is necessary to gather longer term safety and effectiveness information.

Primary Endpoints
An individual subject will be considered a success if they meet all of the following conditions at the 60-month follow-up:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the following for at least two of three domains of the Zurich Claudication Questionnaire (ZCQ):
    - Improvement in physical function by ≥ 0.5 points
    - Improvement in symptom severity by ≥ 0.5 points
    - "Satisfied" or "somewhat satisfied" as defined by a score of < 2.5 points on the patient satisfaction domain
- No re-operations, revisions, removals or supplemental fixation at the index level(s)
- No major implant or procedure-related complications defined as:
    - implant dislodgement as defined in the REP Section 4.8.3
    - migration as defined in the REP Section 4.8.2 causing new or worsened pain or neurological deficit persisting for more than 6 months. If Device migration and symptoms associated with pain or a new or worsened neurological deficit at the index level, the CEC will make final determination if subjects should be followed until the 6 month interval has elapsed since symptom onset.
    - spinous process fracture at the index level(s)
    - deep infection at the operative site requiring hospitalization, surgical drainage, or IV antibiotics
    - death or other permanent disability attributed to the device
    - device component fracture, deformation or disassembled
    - No spinal cord stimulators or rhizotomies
    - No postoperative epidural steroid injections, or nerve block procedures performed to treat spinal stenosis symptoms at the index level(s) determined by the CEC to potentially impact clinical outcomes

Statistical Plan
A Bayesian technique will be used. If the posterior probability of the null hypothesis is at least 95.8%, using uniform priors for each success rate then the claim of non-inferiority will be made. The choice of non-inferiority margin, Δ (i.e., clinically non-significant difference) is 10 percentage points for the overall subject success rate.

Within the current protocol outline that the sponsor has provided, there is no indication that computed tomography will be implemented to evaluate spinous process fractures for any subjects. The FDA believes that CT evaluations need to be conducted among all subjects at 5th year post implant to have a meaningful evaluation of the spinous fractures and their possible relationship to the serious adverse events long term. Based on Kim DH *et al* (2011) [2], "*Interspinous process spacer surgery appears associated with a higher rate of early postoperative spinous process fracture than previously reported. Moreover, in most subjects, fractures were associated with mild or no acute localized pain. This study suggests that unrecognized spinous process fracture may be responsible for a significant number of subjects who experience unsatisfactory outcome after IPS surgery. CT imaging is required to identify the vast majority of such fractures*."

Study 2: New-enrollment study (Actual conditions of use study)

Objective

- To confirm that Superion® performance is not clinically inferior in the PAS population compared to the pivotal IDE Superion® group population. The Month 24 composite clinical success (CCS) endpoint used in the IDE trial will be used in primary analyses to facilitate this comparison.
- To compare clinical status of subjects implanted with the Superion® device relative to surgical decompression 2 years post operatively.
- To evaluate longer term (3 year) Superion® device performance in the actual conditions of use population and to compare this Month 36 composite clinical success between subjects implanted with Superion® relative to decompression.

Study Design and Population

This is multicenter RCT investigation with the following groups: investigational treatment group-stabilization with Superion® InterSpinous Spacer (Superion® ISS) subjects and control group-decompression surgery. Subjects suffering from moderate symptoms of neurogenic claudication secondary to a confirmed diagnosis of LSS at one or two contiguous levels from L1 to L5 who meet all inclusion/exclusion criteria will be enrolled in the study.

The proposed annual follow-up for 3 years among newly enrolled subjects at sites that did not participate in the IDE study may provide further the evaluation of long-term safety and effectiveness of the Superion® InterSpinous Spacer compared to decompression.

The comparator group is decompression surgery. Considering that decompression surgery is the current of standard of care for subjects suffering from moderate symptoms of neurogenic claudication secondary to a confirmed diagnosis of LSS at one or two contiguous levels from L1 to L5, the FDA believes this is an appropriate comparison group.

Hypothesis

- Objective 1: The likelihood of PAS Superion® subjects achieving Month 24 CCS will be compared to the same likelihood as observed within the Superion® IDE study population. For reference, please note that in the IDE study, 95 of 183 Superion® subjects (51.9%, 95% Bayesian credible interval 44.6% to 58.8%) achieved Month 24 CCS.
- Objective 2: To determine that the likelihood of achieving Month 24 CCS is larger for subjects implanted with the Superion® device compared to subjects undergoing decompression. It is hypothesized by the sponsor that Superion® will be superior to decompression in terms of the

proportion subjects expected to achieve Month 24 CCS. Symbolically this is Ho: CCSSuperion – CCSdecomp) ≤ 0 vs Ha: CCSSuperion – CCSdecomp > 0. Ho will be rejected in favor of Ha if the Bayesian posterior probability of superiority exceeds the Objective 2 posterior probability study success criterion.

- Objective 3: To determine the likelihood of achieving Month 36 CCS is larger for subjects implanted with the Superion® device compared to subjects undergoing decompression.

Enrollment Plan and Follow-up
Subjects will be tested annually for 3 years. Subjects will be recruited from sites that did not participate in the IDE study, which will ensure a broader range of surgeons and subjects; however, no details on retention strategies were provided.

Primary Endpoints
An individual subject will be considered a success if they meet all of the following conditions at the 24- and 36- month follow-up:

- Month 24
    - The identical Month 24 CCS endpoint as was used in the IDE will be used to compare PAS results to IDE study results. Month 24 success for this comparison will require a clinically significant improvement in at least two of the three domains of the ZCQ; no reoperations, revisions, removals or supplemental fixation at the index level(s); no major implant or procedure-related complications; no device component fracture, deformation or disassembly; no dislodgement, migration, or deformation, new or persistent worsened neurological deficit at the index level, spinous process fractures, and deep infection, death, or other permanent device attributed disability; no spinal cord stimulators or rhizotomies; and no post-operative epidural steroid injections, or nerve block procedures performed to treat spinal stenosis at the index level(s).
    - The Month 24 CCS for Objective 2 (comparison of Superion® to decompression surgery) will be modified to note that implant-related issues are applicable to the Superion® group only.
- Month 36
    - The Month 36 CCS will be slightly modified to account for failures occurring between 24 and 36 months and to assess changes in clinical status from baseline to month 36. A different approach will be used for lumbar epidural injections in order to avoid calling transient symptom management a device failure, unless there is subsequent re-operation or unless patient status is compromised as reflected in an ODI improvement from baseline that is less than 15%. Therefore, for Month 36 CCS, only lumbar injections occurring within 12 months of the Month 36 visit will indicate Month 36 CCS failure. This is because a lumbar injection within 12 months of the Month 36 visit can confound the Month 36 assessment.

The sponsor is planning to employ X-ray at the start of the study to identify spinous fractures and perform CT scans at 24 months for only symptomatic Superion® subjects. FDA believes that CT evaluations need to be conducted among all Superion® subjects to have a meaningful evaluation of the spinous fractures and their possible relationship to the serious adverse events long term.

Statistical Plan

- To assess Objective 1, subjects will be enrolled at sites that were not involved in the IDE study. The likelihood of PAS Superion® subjects achieving Month 24 CCS will be compared to the same likelihood as observed for Superion® subjects within the IDE study population. In the IDE study, 95 of 183 Superion® subjects (51.9%, 95% Bayesian credible interval 44.6% to 58.8%) achieved Month 24 CCS.
- To assess Objective 2, the primary superiority test will involve determining the Bayesian posterior probability that the likelihood of achieving Month 24 CCS is larger for subjects implanted with the Superion® device compared to subjects undergoing decompression. It is hypothesized that Superion® will be superior to decompression in terms of the proportion subjects expected to achieve Month 24 CCS. Symbolically this is Ho: CCSSuperion – CCSdecomp) ≤ 0 vs Ha: CCSSuperion – CCSdecomp > 0. Ho will be rejected in favor of Ha if the Bayesian posterior probability of superiority exceeds the Objective 2 posterior probability study success criterion. A Bayesian predictive probability sample size re-estimation will be employed.
- To assess Objective 3, the primary superiority test will involve determining the Bayesian posterior probability that the likelihood of achieving Month 36 CCS is larger for subjects implanted with the Superion® device compared to subjects undergoing decompression.

Regarding Objective 1 and 2: FDA has concerns about the usefulness and value of powering this study to Objective 1 (The likelihood of PAS Superion® subjects achieving Month 24 CCS will be compared to the same likelihood as observed for Superion® subjects within the IDE study population). FDA believes that the primary objective in this study should be what the sponsor is currently proposing as their secondary objective (compare clinical status of subjects implanted with the Superion® device relative to surgical decompression two years post operatively), as this objective is clinically more meaningful and interpretable.

We will be asking the Panel to comment on the need for, and elements of a, PAS should FDA determine that this PMA application is approvable.

APPENDIX 1 – POST HOC ANALYSIS OF SPINOUS PROCESS FRACTURE RISK FACTORS

As stated previously, the sponsor conducted a post hoc analysis in an attempt to identify risk factors for spinous process fractures observed in subjects enrolled in this clinical trial.

As shown in Tables A1, A2, A4, and A5, anatomic risk factors associated with spinous process fracture in Superion® ISS subjects included higher disc angle (nominal p-value = 0.018 flexion and nominal p-value = 0.008 extension), and lower L4 spinous process height (nominal p-value = 0.001). Of note, as shown in Table A2, greater spondylolisthesis was not correlated with spinous process fractures incidence in Superion® ISS subjects (nominal p-value > 0.6). Also of note, heavier BMI (nominal p-value = 0.029) and "Shallow" implant placement (nominal p-value = 0.004) were significantly associated with fracture and there was a trend for younger age (nominal p-value = 0.12) and smaller interspinous space height in extension (i.e., "kissing spinous processes") (nominal p-value = 0.14) to be statistically associated.

For X-STOP®, as shown in Tables A1, A3, A4, A5, A6, and A7 below, anatomic risk factors associated with spinous process fracture included greater spondylolisthesis (nominal p-value = 0.025 flexion and nominal p-value = 0.012 extension), smaller interspinous space height in extension (nominal p-value = 0.044) and lower L4 spinous process height (nominal p-value = 0.0004). In addition, "Shallow" implant placement, similar to the Superion® results, was significantly associated with fracture (nominal p-value = 0.014).

Table A1: Demographic Risk Factors Identified for Subjects with Spinous Process Fractures

Risk Factor	Superion®			X-STOP®		
	# with Risk Factor	# Fractures	Rate	# with Risk Factor	# Fractures	Rate
Age <67	91	19	20.9%	108	10	9.3%
Age ≥67	99	12	12.1%	93	7	7.5%
BMI < 29.5	104	11	10.6%	102	9	8.8%
BMI ≥ 29.5	86	20	23.3%	99	8	8.1%
Male	110	16	14.5%	129	9	7.0%
Female	80	15	18.8%	72	8	11.1%

Table A2: Anatomical Risk Factor Analysis for Superion® Subjects, Continuous Variables (mITT)

Measurements	Fracture Patients (by levels treated)		Non-Fracture Patients (by levels treated)		Odds Ratio	p-value
	N[1]	Mean	N	Mean		
Disc Angle (Flexion)	48	7.13	224	5.21	1.46	0.018
Disc Angle (Extension)	48	11.53	225	9.58	1.55	0.008
Spondy (mm, Flexion)	48	-1.15	224	-1.27	0.94	0.670
Spondy (mm, Extension)	48	-0.47	225	-0.28	0.94	0.688
Posterior Disc Height	48	4.68	225	5.04	0.82	0.229
Insterspinous Process Distance (mm, Extension)	45	1.19	192	1.76	0.66	0.075
L4 Spinous Process Height (mm)	48	21.6	196	23.3	0.56	0.001
L4 Spinous Process Width (mm)	50	5.48	215	5.57	0.93	0.650

[1]In 2 level patients, fractures were ascribed to both treated levels, as the predominant fracture location was on the spinous process in between treated levels. This artificially inflates the number of fractures by level, but was necessary to adequately assess risk factors.

Table A3: Anatomical Risk Factor Analysis for X-STOP® Subjects, Continuous Variables (mITT)

Measurements	Fracture Patients (by levels treated)		Non-Fracture Patients (by levels treated)		Odds Ratio	p-value
	N[1]	Mean	N	Mean		
Disc Angle (Flexion)	25	7.50	264	5.78	1.44	0.085
Disc Angle (Extension)	25	11.54	263	10.44	1.29	0.243
Spondy (mm, Flexion)	25	-2.38	264	-0.91	0.64	0.025
Spondy (mm, Extension)	25	-1.42	263	0.15	0.61	0.012
Posterior Disc Height	25	4.75	263	4.67	1.05	0.825
Insterspinous Process Distance (mm, Extension)	23	0.97	234	1.70	0.53	0.044
L4 Spinous Process Height (mm)	24	20.28	235	22.88	0.40	0.0004
L4 Spinous Process Width (mm)	27	5.92	250	5.58	1.27	0.205

[1]In 2 level patients, fractures were ascribed to both treated levels, as the predominant fracture location was on the spinous process in between treated levels. This artificially inflates the number of fractures by level, but was necessary to adequately assess risk factors.

Table A4: Potential Preoperative Radiographic Risk Factors for Spinous Process Fracture

Risk Factor	Superion®			X-STOP®		
	# with Risk Factor	# Fractures	Rate	# with Risk Factor	# Fractures	Rate
L4 Spinous Process Height <21mm	58	13	22.4%	53	8	15.1%
L4 Spinous Process Height ≥21mm	115	12	10.4%	125	6	4.8%
Kissing Spinous Processes[1]	49	12	24.4%	60	7	11.7%
Not Kissing Spinous Processes[1]	216	33	15.3%	250	16	6.4%
Grade 1 Spondylolisthesis	69	13	18.8%	78	10	12.8%
No Spondylolisthesis	121	18	14.9%	123	11	8.9%

[1]Defined as levels with a fracture adjacent with <0.2mm separation in extension. Fractures on 2 level patients in the "middle" spinous process are counted twice.

Table A5: Potential Surgical Implantation Risk Factors for Spinous Process Fracture

Risk Factor	Superion®			X-STOP®		
	# with Risk Factor	# Fractures	Rate	# with Risk Factor	# Fractures	Rate
1 Level Implantation	99	12	12.1%	99	7	7.1%
2 Level Implantation	90	19	19.9%	100	10	10.0%
Device Positioning: Shallow[2]	18	8	44.4%	24	6	25.0%
Device Positioning: Middle[2]	220	33	15.0%	189	11	5.8%
Device Positioning: Deep[2]	8	0	0.0%	37	6	16.2%

[2]Fractures on 2 level patients in the "middle" spinous process are counted twice. Positioning of the device was assessed on post-op images, with the spinous process divided into 3 sections: "Deep" consisting of the anterior 1/3 of the spinous process AP length, "Middle" consisting of the middle 1/3 of the spinous process AP length, and "Shallow" consisting of the posterior 1/3 of the spinous process AP length.

While spinous process fractures were the only radiographic observation in Superion® ISS subjects, X-STOP® subjects exhibited not only spinous process fractures, but migrations, and dislodgements as well, as shown in Table A6. In X-STOP® subjects, these incidences often overlapped, with migration or dislodgement secondary to a spinous process fracture, or migration in conjunction with dislodgement.

Table A6: Characterization of Device Dislodgement in the Superion® IDE

Dislodgement Type	X-STOP®			
	n	% of Dislodgements	% with Migration >5mm	% with Spinous Process Fracture
Complete Dislodgement	6	30.0%	33.3% (2/6)	0.0% (0/6)
Superior Dislodgement Only	9	45.0%	44.4% (4/9)	22.2% (2/9)
Inferior Dislodgement Only	5	25.0%	40.0% (3/5)	40.0% (3/5)

Table A7: Summary Characterization of X-STOP® Risk Factors for Migration and/or Dislodgement

Risk Factor	X-STOP®		
	# with Risk Factor	# Migration/ Dislodgement	Rate
Demographic Risk Factors			
Age <67	108	16	14.8%
Age ≥67	93	8	8.6%
BMI < 29.5	102	7	6.9%
BMI ≥ 29.5	99	17	17.2%
Male	129	14	10.9%
Female	72	10	13.9%
Preoperative Radiographic Risk Factors			
Parallel Spinous Processes	110	9	8.2%
Divergent Spinous Processes	56	6	10.7%
Convergent Spinous Processes	91	7	7.7%
Grade 1 Spondylolisthesis	78	10	12.8%
No Spondylolisthesis	123	14	11.4%
Intraoperative Risk Factors			
1 Level Implantation	99	14	14.1%
2 Level Implantation	100	10	10.0%
Device Positioning: Shallow[1]	24	10	41.7%
Device Positioning: Middle[1]	189	9	4.8%
Device Positioning: Deep[1]	37	3	8.1%

[1]Per level of device position. Positioning of the device was assessed on post-op images, with the spinous process divided into 3 sections: "Deep" consisting of the anterior 1/3 of the spinous process AP length, "Middle" consisting of the middle 1/3 of the spinous process AP length, and "Shallow" consisting of the posterior 1/3 of the spinous process AP length.

Of the three demographic factors considered, Age, BMI, and Gender, it is noteworthy that larger BMI was statistically associated with Migration/Dislodgement (nominal p = 0.02957) and that there was a trend toward Age < 67 having more Migration/Dislodgement. There were no notable findings among preoperative radiographic risk factors, which consisted of morphology (parallel, divergent, or convergent spinous processes) and Grade 1 Spondylolisthesis. Among intraoperative risk factors, "Device Positioning: Shallow" had dramatically higher Migration/Dislodgement events with 41.7% (10/24) of shallow implants having these events. This compares to 4.8% (9/189) of "Device Positioning: Middle" implantations and 8.1% (3/37) of "Device Positioning: Deep" implantations having Migration/Dislodgement events. The nominal p-value (Fisher-Freeman-Halton) for these results was 0.0001.

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